

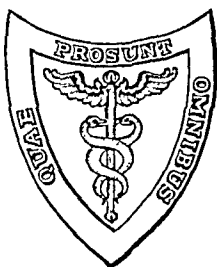
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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

JANUARY, 1937

ORIGINAL ARTICLES.

THE INDEPENDENCE OF CHOREA AND RHEUMATIC ACTIVITY.*

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THE authors' original group of rheumatic patients included 10 individuals who had chorea which appeared to be unrelated to rheumatic activity¹. None of these children developed any other manifestation of rheumatism in the subsequent 5-year period. Furthermore, as the group under observation was enlarged it became evident that chorea frequently occurred in rheumatic subjects without any other clinical or laboratory signs of rheumatic activity. These observations suggested that the customary use of chorea as evidence of rheumatic activity might not be justified. A study of the incidence of chorea in relation to rheumatic activity was therefore undertaken.

The clinical material comprises two groups of patients. The first group consists of 114 patients with chorea that have been seen once a month in our rheumatic clinic for periods of 2 to 10 years. The second group consists of 137 consecutive admissions to the Babies Hospital for chorea.

The findings in these two groups may be summarized briefly. In the rheumatic clinic group, 34 of 114 patients with chorea (approx-

* The work reported in this communication was carried out under The W. K. Kellogg Foundation Fund.

imately 30%) failed to develop any evidence of rheumatic activity other than repeated chorea. In the Babies Hospital group, 69 attacks of chorea occurred in patients without either history or stigmata of rheumatic disease. The other 68 attacks of chorea were in patients who had shown other rheumatic manifestations. However, 29 of these 68 attacks occurred when the rheumatic process appeared quiescent. The remaining 39 attacks of chorea were accompanied by frank manifestations of rheumatic activity. These findings indicate that one-half of all cases of chorea in New York may occur in individuals who are not susceptible to rheumatic fever. Choreic children of this type under our observation developed no stigmata of rheumatic disease although each experienced 1 to 5 attacks of chorea. These individuals did not have a familial history of rheumatic fever. Their attacks were not preceded by respiratory infections, but seemed to be associated with psychic trauma. Their blood sedimentation rates and leukocyte counts were usually normal.

The other half of the cases of chorea occurred in rheumatic subjects. About 40% of these attacks began during quiescence of the rheumatic process. They either followed immediately after fright (*e. g.*, "saw brother killed," "frightened by a mouse," "frightened by man with a gun," "fell on an iron fence," "frightened by seeing playmate killed," "attacked by police dog," "placed behind piano by teacher in school," etc.) or developed insidiously following severe mental strain of school work and examinations. As in the case of non-rheumatic subjects with chorea, these patients had normal blood sedimentation rates and leukocyte counts. The remaining 60% of attacks in rheumatic subjects occurred as a manifestation of disease activity. These attacks followed hemolytic streptococcus infections of the respiratory tract. They were accompanied by other evidences of rheumatic fever, high blood sedimentation rates and leukocytosis.

An illustrative case history of each type is presented in brief:

TYPE 1.—Chorea in Non-rheumatic Subject. Helen E., a girl aged 16, has been under the authors' care for 6 years. At the age of 7 she was attacked by a German police dog, and although not bitten was severely frightened. Then she began to twitch and had difficulty in talking and feeding herself. She experienced another attack of chorea each year until puberty. During the fifth of these attacks she was observed for 3 weeks at the Babies Hospital where the physical signs (other than chorea) and laboratory determinations were all normal. She has escaped all rheumatic manifestations. The sixth attack followed being frightened by a burglar; the others seemed to be associated with school work. She contracted two hemolytic streptococcus infections without sequelae. Since puberty she has been free of chorea.

TYPE 2.—Chorea in Rheumatic Subject During Quiescence. Mary J., a girl aged 16, has been under the authors' care for 5 years. She had frank rheumatic fever and developed mitral stenosis. In November, 1933, she was free of rheumatic manifestations. The blood values, including sedimen-

tation rate and antistreptolysin titer, were normal. During a school inspection by a visiting superintendent at this time, Mary was called upon to recite some poetry. She could not remember her poem and became panic stricken. Within an hour she began to twitch. Within 6 hours she had violent chorea. The attack required restraint in bed for a period of 6 weeks. She developed no manifestation of rheumatic activity and the blood determinations remained normal. Since puberty she has been free of chorea.

TYPE 3.—*Chorea with Activity of the Rheumatic Process.* Dorothy F., a girl aged 11, has been under the authors' care since an attack of rheumatic fever in February, 1933, 9 days after an upper respiratory infection. In June, 1933, she contracted hemolytic streptococcus pharyngitis which was followed 2 weeks later by fever, with leukocytosis, elevation of blood sedimentation rate and rise in antistreptolysin titer, and then frank chorea with night terrors. She was re-infected with hemolytic streptococcus in April, 1934, and 3 weeks after recovery from pharyngitis developed another attack of chorea and carditis with elevated blood sedimentation rate and an increase in antistreptolysin titer. Although only 10 years old, she began to menstruate during this attack and subsequently escaped chorea. She was reinfected with hemolytic streptococcus in January, 1935, and 2 weeks later developed another attack without any evidence of chorea.

Discussion.—Two reports bearing on this subject have recently appeared. Gerstley, *et al.*,³ in Chicago, in a study of 150 children with chorea "suggest that chorea should not be taken as an indication of rheumatic infection without other rheumatic manifestations." Jones and Bland⁵ analyzed 1000 consecutive cases of juvenile rheumatism at the House of the Good Samaritan in Boston. They found that 73% of their patients with chorea and other rheumatic manifestations developed heart disease; while only 3% of those having chorea without other rheumatic manifestations developed heart disease. Twenty-eight per cent of all their cases had "pure chorea."

As has just been pointed out, in our rheumatic clinic approximately 30% of patients with chorea developed no evidence of rheumatism. This is in good agreement with the incidence of "pure chorea" found by Jones and Bland. Our observations are entirely in accord with those made independently in Chicago and Boston.

The observations just presented are based on clinical criteria. There is also evidence of a more objective character that chorea is not pathognomonic of active rheumatism. The blood sedimentation rate is generally recognized as a highly sensitive index of rheumatic activity; yet in our experience and in that of a number of other observers^{2,4,6,7,8} uncomplicated chorea, even in patients known to be susceptible to rheumatic fever, is accompanied by normal sedimentation rates. This in our opinion is strong evidence against the rheumatic origin of chorea.

In the past we have emphasized the great variety of manifestations that occur in the rheumatic state.¹ This was done for the purpose of throwing light on the character of the disease process. It is well recognized that the minor rheumatic phenomena are non-specific. It becomes increasingly evident that chorea, which has been considered a major manifestation, is not pathognomonic of

rheumatism. The present observations indicate that in New York City about three-quarters of all chorea is independent of rheumatic activity. It is the authors' opinion that the physiological background prerequisite to the development of chorea may be prepared by a number of abnormal conditions but is especially well prepared by the rheumatic state. This accounts for its frequency in rheumatic subjects. However, the factor which initiates the attack of chorea can be entirely independent of rheumatic activity.

Summary. 1. One-half of the cases of chorea under observation occurred in non-rheumatic subjects.

2. Approximately one-fourth of the cases of chorea occurred in quiescent rheumatic subjects.

3. Approximately one-fourth of the cases of chorea occurred during active rheumatism.

4. Uncomplicated chorea is accompanied by normal blood sedimentation rates.

5. Chorea *per se* does not suffice for the recognition of the rheumatic subject nor for the diagnosis of rheumatic activity.

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NOTE ON THE DURATION OF SYMPTOMS AND AGE AT DEATH IN CHRONIC RHEUMATIC VALVULAR DISEASE, ESPECIALLY IN TRICUSPID STENOSIS.*

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AN analysis of cases examined postmortem at this hospital† has impressed us with certain features of the clinical course of patients dying with rheumatic heart disease which are little appreciated and deserve emphasis. Figures similar to the ones we shall present have already been published by Laws and Levine,² taken, in fact,

* Aided by a grant from the Proctor Fund of Harvard University for the Study of Chronic Diseases.

† All the patients under consideration were more than 12 years of age, as younger children are not admitted to this hospital.

from the same autopsy material. Further consideration of the cases included by them has shown that in a fair proportion the valvular deformity was slight and scarcely significant clinically. Our rearrangement has been such as to include only cases with unequivocal organic valvular deformity of a degree sufficient to make its clinical recognition reasonable. This series is therefore applicable to patients still living and in whom valvular deformity may be recognized with some certainty. An objection may be made to the inclusion here of cases of tricuspid stenosis when we speak of recognizable deformities. It is true that a definite diagnosis of tricuspid stenosis was made clinically in but 2 of the 21 instances of its occurrence, and that organic tricuspid disease was suspected in only 6. It is the features of these very patients which constitute the chief reason for this note, for only through an appreciation of such factors as we shall present will our diagnostic capabilities in regard to tricuspid stenosis be enhanced.

Age at Onset of Symptoms. It is now well known that symptoms of cardiac insufficiency in patients with aortic stenosis do not appear, as a rule, until comparatively late in life. Our figures in regard to this lesion play only a confirmatory rôle. The patients with mitral stenosis, alone or in combination with aortic valve disease, began their inevitable downhill course about 10 years earlier in life. It is the group with tricuspid stenosis, however, that is most striking, symptoms having appeared in them when they were more than 20 years younger than those with aortic stenosis alone. The cases with tricuspid stenosis in this series, which includes all those examined postmortem during a 22-year period at this hospital, had also mitral stenosis in every instance and a number of them had aortic valve disease as well. The early appearance of symptoms in a patient with mitral stenosis, with or without aortic involvement, points, then, in the absence of active rheumatism, to the possibility of the additional presence of stenosis of the tricuspid valve.

TABLE 1.—EFFECT OF THE TYPE OF VALVULAR INVOLVEMENT ON DURATION OF SYMPTOMS AND AGE AT DEATH.

	No. of cases.	Average age at onset of symptoms.	Average age at death.	Average duration of symptoms, years
Aortic stenosis (with or without insufficiency)	43	50.4	53.5	3.1
Mitral stenosis (with or without insufficiency)	24	41.5	46.25	4.6
Aortic and mitral involvement	77	37.0	42.1	5.1
Tricuspid stenosis (with other valve involvement)	21	26.9	34.4	7.5

Duration of Symptoms. Again our figures are only confirmatory of the well known fact that patients with aortic stenosis, once failure supervenes, die quickly. The average duration of life after the onset of symptoms of these patients in our series was only about

3 years. Those with mitral valve deformity, either alone or in combination with aortic valve involvement, lived somewhat longer, while those with tricuspid stenosis lived much longer after the onset of symptoms than any of the other groups. There is less difference, therefore, in the average ages of the groups at the time of death than in the average age at the onset of symptoms.

Comment. Although this note concerns patients who already exhibit heart failure, and presents data with respect to life expectancy and age at death, there are certain inferences which are applicable to ambulatory and well compensated valvular patients. If a patient is seen with aortic stenosis unassociated with other valvular disease and free from cardiac symptoms, one may expect satisfactory function of the circulation to continue until comparatively late in life, but a short span of life when failure develops. If, however, a case can be diagnosed as having both mitral and aortic involvement, although at the moment compensation is adequate, heart failure is apt to intervene at a younger age and will be tolerated longer. Finally, it is doubtful with our present knowledge that we shall be able to recognize the presence of tricuspid stenosis at a stage when the circulatory efficiency is normally compensated. It may be that with greater interest in this question, it will be found that undue enlargement of the right auricle will serve as an early evidence of tricuspid stenosis before hepatic engorgement occurs, just as a similar enlargement of the left auricle in mitral stenosis antedates other evidence of congestion. If such a development occurs, one may then say that a compensated case with tricuspid valve disease will begin to have cardiac disability at a very early age and will tolerate it a long time.

We are aware that there are certain discrepancies between our figures and those presented by DeGraff and Lingg,¹ who found that the duration of life after the development of symptoms or of congestive heart failure was "about the same regardless of the valve or the number of valves affected." Since postmortem examinations were carried out in only 13% of their cases, their figures and conclusions can scarcely be applied to the tricuspid valve, as deformity of this valve is usually overlooked clinically at the present time.

The earlier literature on tricuspid stenosis is filled with debates on the acquired *versus* congenital origin of this lesion, while now probably no one holds the congenital origin as tenable for the great majority. Our figures, showing as they do the early appearance of symptoms in patients with stenosis of this valve, perhaps shed some light on the reason for the previous adherence of many to the idea of congenital origin.

A striking clinical feature of the patients with tricuspid stenosis was the predominance of ascites and enlargement of the liver without peripheral edema or congestion of the lungs. One patient was admitted to the hospital 20 times, and abdominal paracentesis

was performed 34 times. It seems reasonable to suppose that the mechanism, whatever it may be, of this affinity for the abdomen as the site for the accumulation of fluid is similar to that seen in chronic constrictive pericarditis (Pick's disease), in which there is an obstruction to the diastolic filling of the heart. This latter entity, so well described by White,³ is associated with a kind of congestion quite different from that seen in ordinary congestive failure. Tricuspid stenosis should be no less effective in preventing the natural filling of the right ventricle (and therefore of the left cavities as well) and thereby producing a chronic elevation of venous pressure than is a thickened callous pericardium surrounding the right auricle at its attachment to the venæ cavæ, so common in Pick's disease.* Further observation of patients with stenosis of this valve in life will, we predict, show many similarities with Pick's disease. The evidences of congestion in tricuspid stenosis are in part, therefore, the result of mechanical factors like those present in chronic constrictive pericarditis, and not entirely due to myocardial insufficiency.

Summary and Conclusions. We have found that patients with tricuspid stenosis, in spite of the fact that death occurs at a comparatively early age, are able to tolerate their symptoms considerably longer than are those patients in whom the tricuspid valve is not involved. The average figures are, therefore, somewhat paradoxical and contrary to what one might expect. We have attempted to point out, however, that in tricuspid stenosis the symptoms and signs are not wholly due to myocardial failure, and that they are in part due to mechanical obstruction to the normal diastolic filling of the heart, so that this apparent paradox is in part, at least, explained.

We believe that our figures contribute two important clues to the diagnosis of tricuspid stenosis: first, the appearance of symptoms at an early age in patients with chronic rheumatic valvular disease; and second, an ability to carry on with such symptoms for an unusually long time, particularly when the prominent features are enlargement of the liver and ascites. If these features cause us to *suspect* tricuspid stenosis, we are then one step nearer the goal of making accurate antemortem diagnoses.

NOTE.—Since this paper was prepared for publication, a case of rheumatic heart disease with mitral stenosis has come to autopsy at the Massachusetts General Hospital in which one of us was enabled, partly on the basis of the material here presented, to predict accurately the additional finding of tricuspid stenosis.

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* A similar view was expressed by Drs. C. Sidney Burwell and Paul D. White in personal communications.

STUDIES IN DIABETES MELLITUS.

V. HEREDITY.

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HEREDITY is an important force in the etiology of diabetes, but its rôle is somewhat obscured by other factors. These are so interwoven in their operation that it is difficult to isolate the effect of any single one. The situation is, moreover, complicated by the fact that we are concerned in diabetes not so much with the inheritance of the disease as with the inheritance of constitutional abnormalities which predispose the individual to the disease. This predisposition is usually not revealed much before the actual onset of the disease, which is most frequent in middle and later life. We are thus confronted with the problem of what may be called the "carrier," who may not himself develop diabetes, but who nevertheless transmits the predisposition to his children. Consequently, it is impossible to identify all the "carriers" in the family history, and this impairs the record.

The chief reasons for failure to identify "carriers" are as follows: (1) Cases of diabetes in the family which do not develop characteristic symptoms and consequently are never diagnosed; (2) cases which develop symptoms but escape diagnosis; (3) cases which are diagnosed but are not specified in the patient's record because he does not know this feature of his family history; (4) cases that fail to be identified because the "carrier" in the family did not survive to the age at which diabetes would ordinarily manifest itself; (5) cases in which the potential "carrier," still living, has not yet, but will later, become diabetic; (6) cases where the "carrier" dies without issue; and (7) cases which have developed since the original examination of the patient, but are not known because direct contact with the patient has ceased.

With these limitations to the data in mind, let us examine first the crude figures on the family history of diabetics as a group, and later the more refined analyses. In this experience cases have been classified as having a positive family history of diabetes only if the affected relative comes within a restricted degree of relationship, the cases being classified as "hereditary" or "familial" as follows: (a) Hereditary—cases with a diabetic parent, grandparent, uncle,

aunt, nephew, niece or child; (b) familial—cases with a diabetic brother, sister or first cousin. All cases in which the reported diabetes in the relative was questionable were excluded from the count of positive histories. The record is not as complete as it could be, for only in the last 5 years or so have patients been questioned regarding their family history on each visit. The facts are presented in detail, but we believe that the maximal figures, within the limits of error due to chance, come fairly close to portraying the true picture. The proportions quoted for hereditary cases include those in which familial diabetes also occurs, but the proportions for familial exclude cases where both types exist. Figures are presented separately, however, for such cases.

This classification of family histories as "hereditary" or "familial" is that conventionally used in medical literature. It does not conform strictly with the present-day terminology used in the study of heredity. It is useful, however, in summarizing the incidence of diabetes in the direct and collateral lines. For, it demonstrates the importance of age upon the occurrence of diabetes in the relatives. Those diabetic relatives included in the hereditary group are older, on the average, than those in the familial or collateral relatives. Consequently, younger diabetics show a higher incidence of hereditary type cases than familial, whereas, in older diabetics, the proportions are more nearly equal.

On the basis described, there were, among all patients seen between 1897 and 1928, 1,559 (24.5%) who reported 1 or more diabetics in their family. Of this number, 1,011 (15.9%) gave a hereditary history and 548 (8.6%) a familial history. In 210 cases (3.3%) both types of family history were reported. The reported instances included all known at or about the 1929 anniversary of discharge, except in the case of children for whom the known facts up to 1935 are included.

The facts on the group, as already indicated, really understate the incidence of a family history of diabetes, for the ascertained frequency of positive family histories is greatest in the more recent patients. Thus, among patients first seen in 1925-1928, 26.3% gave family histories of either type, compared to 24.7% in 1920-1924, 24% in 1915-1919 and only 18% in patients first seen prior to 1915. Furthermore, as Table 1 shows, the increase is in histories of the hereditary type.

Analysis of the facts by sex and age shows that even the relatively high figure for recent cases is an incomplete measure of the importance of heredity. Women, who tend to take more interest in the details of family history and probably know more about them, consistently report a higher family incidence of the disease than do men. Thus, among adult patients, 20 years or over at examination, 23% of the men and 26.5% of the women reported positive family histories. A margin in favor of the females was found consistently

in the several calendar year periods detailed in the preceding paragraph.

TABLE 1.—INCIDENCE OF DIABETES IN THE FAMILIES OF DIABETICS. PERCENTAGE OF CASES REPORTING HEREDITARY AND FAMILIAL TYPES OF FAMILY HISTORY. EXPERIENCE OF E. P. JOSLIN, 1897-1928.

Year of examination.	Per cent with family history of diabetes.				No. of cases.
	Total hereditary and/or familial.	Total hereditary.*	Familial only.	Hereditary and familial.	
Total, 1897-1928	24.5	15.9	8.6	3.3	6,357
1925-1928	26.3	17.8	8.5	3.7	2,689
1920-1924	24.7	15.7	9.0	3.0	2,162
1915-1919	24.0	14.5	9.5	3.6	799
1897-1914	18.0	11.0	7.0	2.5	727

* Includes cases with familial type also.

Children, particularly in the years since insulin was discovered, with whom satisfactory contact can now be kept up and whose family histories are most up to date, show an extremely high frequency of diabetes in the family. In children up to age 15 at onset, seen during the years 1929 to 1931, 39.5% of the boys and 33.8% of the girls reported 1 or more cases of diabetes in the family, of which 28.6% and 28.5%, respectively, were of the hereditary type, described above. These percentages tend to be high in all except the very early and the very recent cases (Table 2). The low incidence is due to the short period of observation; in the earlier period because of the short duration of life of these children. We have also segregated certain groups of living children, and it will be noticed that the figures for them generally run high.

Distinct differences according to age in the proportions reporting positive family histories are likewise found in adult diabetics (Table 3). The proportions among males varied from a minimum of 18.9% at ages 65 and over, to a maximum of 25.9% at ages 45 to 54 and 25.4% at 35 to 44. Among females, the minimum was 22.7% at ages 20 to 34 and the maximum, 32.1% at 45 to 54. The figures for recent years are even higher. It may be noted, however, that the percentages are not much lower for patients seen in the 10 years preceding 1925, probably due to the longer period of observation on many of these earlier cases.

Significant differences are also found in the types of family histories at the several ages. Among children and younger adults, hereditary type histories greatly outnumber the familial types. There is a distinct tendency for the percentage of patients with hereditary type histories to decrease with the age of the patient, but the percentage with familial type histories increases, and in older patients the proportion of these cases approaches or even exceeds histories of the hereditary type. These tendencies, as

Table 3 also shows, exist both in recent cases and those first seen in the earlier years of this experience.

TABLE 2.—INCIDENCE OF DIABETES IN THE FAMILIES OF CHILD DIABETICS (AGE 15 OR LESS AT ONSET). PERCENTAGE OF CASES IN SPECIFIED PERIODS REPORTING HEREDITARY AND FAMILIAL TYPES OF FAMILY HISTORY. BY SEX. EXPERIENCE OF E. P. JOSLIN, 1897-1934.*

Year of examination.	Per cent with family history of diabetes.						No. of cases.†	
	Males.			Females.			Males.	Females.
	Total hereditary and/or familial.	Total hereditary.†	Familial only.	Total hereditary and/or familial.	Total hereditary.†	Familial only.		
Total children,								
1897-1934 . . .	30.9	23.0	7.8	28.5	25.2	3.3	486	456
1932-1934 . . .	24.3	18.9	5.4	17.3	17.3	...	111	98
1929-1931 . . .	39.5	28.6	10.9	33.8	28.5	5.4	119	130
1925-1928 . . .	33.7	23.1	10.6	29.0	25.2	3.7	104	107
1920-1924 . . .	34.0	26.6	7.4	34.6	32.1	2.6	94	78
1915-1919 . . .	14.7	11.8	2.9	32.1	25.0	7.1	34	28
1897-1914 . . .	16.7	16.7	...	13.3	13.3	...	24	15
Living children only (Jan. 1, 1934);								
Total, 1897-1934	34.5	26.3	8.3	30.0	26.7	3.3	339	337
1932-1934 . . .	27.8	20.8	6.9	18.8	18.8	...	72	64
1929-1931 . . .	38.4	28.6	9.8	33.3	28.5	4.9	112	123
1897-1928 . . .	34.8	27.1	7.7	32.0	28.7	3.3	155	150

* Family history as of date of last contact with child or his family.

† Includes cases with familial type also.

‡ Excludes adopted children and others with incomplete family history.

These differences bring out the incompleteness, usually unavoidable, of these histories. Thus, the low ratios of the hereditary histories, reported by old patients, reflect the failure to identify cases of diabetes in their parents or grandparents because most of these relatives died years ago when the diagnosis of the disease was less common than in recent years. Moreover, the subsequent development of diabetes in children of these old patients, which would increase the ratio of hereditary histories among them, is often not reported. On the other hand, familial histories in older patients are on the whole, better reported because the relatives in this group are largely of the same generation as the patient, and, consequently, a large proportion of these relatives have reached the "diabetes age." Among younger patients, the higher figures of the hereditary type histories reflect better reporting or diagnosis of diabetes in the parents and grandparents, because in this case the relatives are either still living or fairly recently deceased. Yet, even in these younger adult patients, the true or complete incidence of hereditary cases cannot be known for many years, since their children are usually not yet old enough to have developed any considerable number of cases of the disease. In like manner, the incidence of familial diabetes in these younger patients is low, because the younger the patient, the smaller the proportion of

relatives in this class who have reached the ages at which diabetes most frequently occurs.

TABLE 3.—INCIDENCE OF DIABETES IN THE FAMILY HISTORY OF ADULT DIABETICS, IN RELATION TO AGE OF THE PATIENT. PERCENTAGE OF CASES REPORTING HEREDITARY AND FAMILIAL TYPES OF FAMILY HISTORY. BY SEX AND CALENDAR YEAR PERIODS AT EXAMINATION. EXPERIENCE OF E. P. JOSLIN, 1897-1928.

Year and age at examination.	Per cent with family history of diabetes.								No. of cases.	
	Males.				Females.					
	Total.	Total hereditary.*	Familial only.	Hereditary and familial.	Total.	Total hereditary.*	Familial only.	Hereditary and familial.	Males.	Females.
<i>Total, 1897-1928</i>	23.0	14.5	8.5	2.8	26.5	16.8	9.7	4.0	2,779	2,914
Ages 20 and over . . .	23.2	17.2	6.0	3.0	22.7	17.5	5.2	4.9	401	286
20-34	25.4	17.5	7.9	2.4	27.2	18.3	8.9	4.5	418	382
35-44	25.9	17.6	8.3	2.2	32.1	22.6	9.5	4.0	723	791
45-54	21.2	11.8	9.4	3.8	23.1	12.5	10.6	4.3	709	928
55-64	18.9	9.1	9.8	2.3	25.6	14.2	11.4	2.8	438	527
65 and over . . .										
<i>1925-1928</i>										
Ages 20 and over . . .	24.7	16.5	8.2	3.3	27.7	18.4	9.3	4.4	1,091	1,315
20-34	24.1	17.9	6.2	3.4	27.0	23.0	4.0	8.0	145	100
35-44	28.3	23.5	4.8	4.1	29.9	22.0	7.9	3.7	145	164
45-54	30.9	22.6	8.3	3.0	32.5	23.7	8.8	4.0	265	351
55-64	21.9	12.9	9.0	3.4	24.0	13.5	10.5	4.8	324	438
65 and over . . .	19.3	9.0	10.3	2.8	26.3	15.6	10.7	3.4	212	262
<i>1920-1924</i>										
Ages 20 and more . . .	22.5	14.2	8.3	3.1	26.4	15.8	10.6	2.9	906	1,032
20-34	26.8	18.8	8.0	2.9	22.7	15.5	7.2	3.1	138	97
35-44	22.2	14.1	8.1	2.2	24.2	16.6	7.6	4.5	135	132
45-54	23.0	14.1	8.9	2.1	34.1	22.7	11.4	3.1	235	290
55-64	21.3	13.6	7.7	4.8	22.0	10.0	12.0	2.3	272	311
65 and over . . .	19.8	11.1	8.7	2.4	25.6	15.1	10.5	2.3	126	172
<i>1915-1919</i>										
Ages 20 and over . . .	25.5	15.0	10.5	2.3	25.7	15.5	10.2	5.9	400	304
20-34	19.4	14.6	4.8	3.2	15.9	11.4	4.5	..	62	44
35-44	30.7	21.4	9.3	1.3	29.8	21.3	8.5	8.5	75	47
45-54	26.5	16.8	9.7	1.8	26.3	16.3	10.0	6.3	113	80
55-64	26.3	12.6	13.7	4.2	26.1	15.9	10.2	8.0	95	88
65 and over . . .	21.8	7.3	14.5	..	28.9	12.1	17.8	4.4	55	45
<i>1897-1914</i>										
Ages 20 and over . . .	16.2	8.6	7.6	1.3	22.1	14.5	7.6	4.6	382	263
20-34	16.1	14.3	1.8	1.8	20.0	15.6	4.4	6.7	56	45
35-44	19.0	6.3	12.7	..	23.1	5.1	18.0	2.6	63	39
45-54	19.1	13.6	5.5	0.9	28.6	24.3	4.3	5.7	110	70
55-64	13.9	2.8	11.1	1.9	18.0	14.7	3.3	6.6	108	61
65 and over . . .	11.1	6.7	4.4	2.2	18.8	6.3	12.5	..	45	48

* Includes cases with familial type also.

Family Incidence of Diabetes in Other Experiences. Several other observers have reported a high frequency of diabetes in the families of their diabetic patients. Table 4 summarizes several of the more recent experiences.^{2,3a,3b,6,7,9,12,14,15,16,18,21,23} It is not certain, however, to what extent the figures are comparable because the definitions or inclusions are not always the same. Unfortunately, statements regarding this important detail are rarely given, and, in some cases,

at least, the inclusions are not as strictly limited as in this experience. Other factors that impair comparability are the type of patients, *i. e.*, whether private, clinic or ward, the sex and age distribution, and also the length of the period of observation of the patients. Despite these limitations, it is significant that in several of the experiences shown in the table, the percentages of patients with a family history of diabetes are nearly of the same order as in the present experience, and in 1 of them, the later series reported by Cammidge, the percentage is considerably higher. Only the series reported by Matz, by Wendt and Peck and by John are much below the average.

TABLE 4.—INCIDENCE OF DIABETES IN THE FAMILIES OF DIABETICS PERCENTAGE OF CASES REPORTING HEREDITARY AND FAMILIAL TYPES OF FAMILY HISTORY. RECENT CLINICAL EXPERIENCES

	Per cent with family history of diabetes			No of cases
	Total hereditary and/or familial	Hereditary	Familial	
Joslin, Boston—1920-1928	25.6	16.9	8.7	4,831
Birach, ² Pittsburgh—1923-1926	19.4			350
Cammidge, [*] London 1934† ^{3b}	39.6	19.9	19.7	1,000
1928† ^{3a}	28.0			800
Gray and Sansum, ⁹ Santa Barbara—1925-1931	23.9	..		1,005
John, ⁹ Cleveland—1921-1928	9.9	5.4	4.5	2,000
1925-1927	10.0	6.1	3.9	1,000
1921-1925	9.7	4.6	5.1	1,000
Kern, ¹⁰ Philadelphia—1934†	25.3	.		300
Labbé, ¹¹ Paris—1931†	27.6	.		557
Lawrence, ¹² London—1930†	28.0	.		1,100
Matz, ¹⁴ U S Veterans' Bureau—1936†				
Living	7.7	4.3	3.4	1,173
Fatal	7.2	4.0	3.2	250
Murray-Lyon, ¹⁶ Edinburgh—1933†	16.3			1,700
Palmer, ¹⁸ Seattle—1919-1929	20.0	12.0	9.0	300
Umler Clinic, Berlin				
Müller, ¹⁵ —1931-1933	25.4			1,372
Finke ⁶ —1925-1930†	26.2	18.7	7.5	1,500
Seckel ²¹ —1920-1925	26.4	17.1	9.0	391
Wendt and Peck, ²³ Detroit—1919-1929	14.8			1,073

* Evidently includes cases with family history of glycosuria

† Publication date

‡ Calculated from figures in text of original article

There is fairly close agreement also between the several series in the percentages of family histories of the hereditary type. Such histories, in most instances, are considerably more frequent than familial type histories, the only exceptions to this rule being the series reported by Cammidge and 1 of John's series. These two observers likewise are the only ones who report more than one series of cases. Cammidge's later group^{3b} shows so large an increase in the reported family incidence of the disease over the earlier group that it must certainly be due to more careful history taking or a difference in definition.

Most observers report higher figures for children than for adults,

and as Table 5 shows, the figures are frequently very high.^{2b,15,6,21,8,20,17} In only 3 of the experiences included in the table are details available regarding the type of family history, and these show considerable differences in this regard.

TABLE 5.—INCIDENCE OF DIABETES IN THE FAMILIES OF CHILD DIABETICS. PERCENTAGE OF CASES REPORTING HEREDITARY AND FAMILIAL TYPES OF FAMILY HISTORY. RECENT CLINICAL EXPERIENCES.

	Total hereditary and/or familial.	Hereditary.	Familial.	No. of cases.
Joslin, Boston—1925-1934	30.0	23.9	6.1	669
Cambridge, ⁸ London—1934*	65.2	19.6	45.5	112
Grote, ⁸ Frankfort—1933*	53.2	65
Priesel and Wagner, ²⁰ Vienna—1932	36.3	16.5	19.8	121
Von Noorden, ¹⁷ Frankfort and Vienna	37.3	102
Umber Clinic, Berlin:				
Müller ¹⁵ —1931-1933	26.9	26
Finke ⁶ —1925-1930	18.0	50
Seckel ¹¹ —1920-1925	39.3	28

* Publication date.

Several aspects of Müller's experience are of interest. His child diabetics showed approximately the same incidence of positive family histories as older patients. Of 181 siblings of his patients, 51 (28.2%) were diabetic; but of the 99 siblings who were approximately the same age or older than the patient, 31.3% had diabetes, compared to 24.4% among younger siblings. This indicates clearly that complete facts on the incidence of diabetes in families of these patients cannot be known because so many of the diabetic relatives will not become diabetic for many years after the original observation in the family. Müller reported also that where neither parent of his patient was diabetic, the incidence of diabetes in the siblings was 14.6%, compared to 25.4% where 1 parent was diabetic and 32% where both parents were diabetic.

A somewhat different type of statement on heredity is that of Faelli,⁵ not included in the table, who reported on the incidence of diabetes in 218 children of 50 diabetic patients. Of the living children, 21 (9.6%) were diabetic and 14 non-diabetics were obese.

Jewish Diabetics. The incidence of diabetes in the families of the Jewish diabetic patients in this experience is appreciably higher than among other patients. Of the adult Jewish patients, 248 (29.6%) reported 1 or more cases of diabetes in the family, as compared to 24.5% for all patients. The difference between Jewish and non-Jewish patients in regard to their family history of diabetes is particularly marked among males. The percentage of positive family histories was 30.3% for Jewish males, compared to 23% for all males, whereas among females the incidence in Jewish cases was 29.1%, compared to 26.5% for total female cases. It will be noted that contrary to the experience as a whole, Jewish males reported a slightly though not significantly higher incidence of diabetes in

the family than did Jewish females. The higher incidence of family histories of diabetes among Jewish patients has been consistent throughout the experience. This is true for both sexes with but a minor exception.

Among Jewish males, histories both of the hereditary and familial types are more frequent than in non-Jewish male patients. In females, on the other hand, the incidence of family histories of the hereditary type is slightly less in the Jewish group than in the non-Jewish group, but there is an appreciable excess of familial diabetes among the Jewish women.

The greater frequency of positive family histories among Jewish, as compared with non-Jewish patients, is generally more marked at ages under 45 than after that age. It occurs, however, even at some of the more advanced ages. It is notable that the percentage of positive family histories among Jewish male patients is distinctly higher at the younger ages and decreases rather perceptibly with age. Among Jewish females, however, the variation by age in this respect is relatively small.

Another significant finding is that the incidence of hereditary type histories at the younger ages is definitely higher among the Jewish patients than non-Jewish patients, whereas at the older ages the reverse is true. On the other hand, Jewish patients, regardless of age, report a higher incidence of cases of the familial type.

Among Jewish children, in common with diabetic children in general, the percentage of positive family histories is higher than among adults. Of 80 Jewish children whose family histories were recorded, 34 (42.5%) reported cases of diabetes in their families. Hereditary type histories predominated, being reported by 35% of Jewish children. These percentages were somewhat higher than those reported for all children.

Even higher percentages of positive family histories among Jewish patients appear in recent German experiences. Müller¹⁵ reports that 33% of his Jewish patients have diabetic relatives, compared with 25.4% for all patients. Finke⁶ reports 55% among the Jewish, compared with 26.2% for all patients. Among Jewish children, Priesel and Wagner²⁰ report 48% with diabetic relatives, compared with 27.3% for non-Jewish children.

Physicians, Nurses and Dietitians. Additional evidence of the importance of heredity is the high incidence of diabetes in the families of physicians, nurses and dietitians who undoubtedly are better acquainted with their family histories. Of 163 physicians, 28.2% reported 1 or more cases in the family, as compared with 23% for all adult male diabetics. Hereditary type histories were reported by 21.5% of the physicians, but of this group 8% reported familial histories also in addition to 6.7% who reported familial cases only.

Among 49 nurses and dietitians (all females), 34.7% reported positive family histories of diabetes, as compared with 26.5% for all

females. The number of diabetic relatives was large. Thus, 24.5% of the group gave hereditary type histories, but in 12.2% both hereditary and familial cases existed, and in 10.2% familial cases only.

Comparative Incidence of Diabetes in the Families of Diabetics and Non-diabetics. While these figures on the proportion of diabetic patients with diabetic relatives are impressive, they have little meaning by themselves. For, the number of relatives of the patient may be rather large and, purely as a matter of chance one or more of the relatives might be expected to have diabetes in a large proportion of the cases. The problem is, therefore, to compare the actual incidence of diabetes in these families with the expected, based on the incidence in the general population.

A complete solution of this problem requires two types of information: (1) Such genealogic details for diabetic patients as the number of relatives according to sex, the present ages of the living, the ages at death of the deceased and the number and identity of those who were diabetic; and (2) representative data on the incidence of diabetes in a general population according to sex and age. Significant results may, however, be obtained by comparing the incidence of diabetes in the families of diabetics with that in a series of controls, and also by studying the incidence of diabetes in the parents and grandparents of diabetics, a method which fixes accurately the size of the observed population.

A comparison of the incidence of diabetes in the immediate families of diabetic patients in the present series and in a series of controls (consisting of non-diabetic patients, students and nurses), based on the figures reported by Pincus and White,^{19b} appears in Chart I. Because of differences in the age constitution of the diabetic and control series, separate comparisons were made for broad age groups. The facts are shown separately for parents and siblings of the two groups. The facts relate to 1,617 parents and 2,835 siblings of 822 diabetics, and 427 parents and 862 siblings of 217 controls.*

TABLE 6.—COMPARATIVE INCIDENCE OF DIABETES IN THE FAMILIES OF DIABETICS AND NON-DIABETICS. RECENT CLINICAL EXPERIENCES.

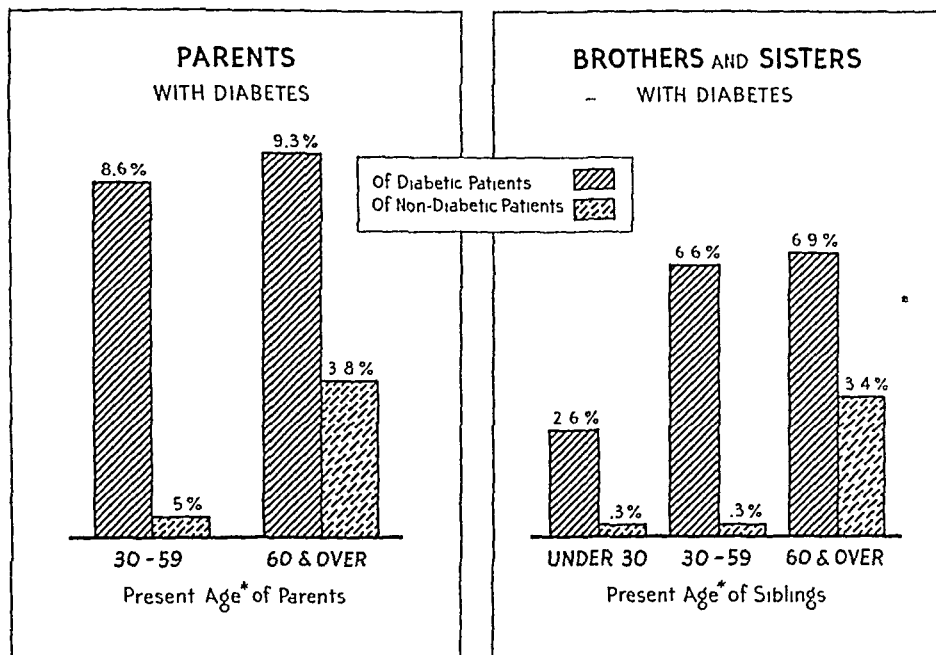
	Per cent with family history of diabetes.		No. of cases.	
	Diabetics.	Non-diabetics.	Diabetics.	Non-diabetics.
Cambridge, ²⁰ London—1931† . . .	39.6	3.4	1,000	500
Finke, ⁶ Berlin—1925-1930 . . .	26.2	3.8	1,500	1,000
Kern, ¹⁹ Philadelphia—1934† . . .	25.3	6.2	300	500

* Parents under 30 years of age excluded.

† Publication date.

The analysis of these histories shows a far greater percentage of diabetic relatives within the immediate families of the diabetic patients than of the controls. This was true both of the parent and sibling comparisons regardless of age. As Chart I shows, the differences were greater at the younger ages in both parent and sibling comparisons. The differences were statistically significant.

Other recent observers^{3b,10,6} have reported similar findings (Table 6). The data are not strictly limited to the immediate families as is the present experience.



* Age at death if deceased

CHART I.—Comparative incidence of diabetes in parents and siblings of diabetic and non-diabetic patients. (Experience of E. P. Joslin, 1934, as reported by Pincus and White.)

Incidence of Diabetes in Twins. Other important evidence of the force of heredity in diabetes is the occurrence of the disease in the members of 29 pairs of twins in the present series, previously reported by White, Joslin and Pincus.²⁴ In 9 out of 13 pairs of similar twins, both members were diabetic, whereas in only 2 out of 16 of dissimilar twins were they both diabetic. The age at onset of diabetes for each member of the similar twins usually differed, but in only 3 out of 9 cases was the difference greater than 10 years. The figures necessarily exclude pairs of twins in which 1 of them died in infancy or early childhood from diseases other than diabetes.

Actual and Expected Incidence in Direct Ancestry of Diabetic Children. The actual and expected incidence of diabetes in the parents and grandparents has been studied for child diabetics. We have computed the expected number of diabetics among the parents and

grandparents, derived from analysis of life tables by causes of death according to population mortality statistics. The estimate of the expected number is the sum of the products of the number of children times the separate probabilities of dying from diabetes for (1) the father, (2) the mother, (3) both grandfathers and (4) both grandmothers. For grandparents, we have used the probabilities at age 25, and for parents, the probabilities of dying from the disease between 25 and 70. Age 25 was chosen because it is roughly the average age of parents at the birth of the first child. (This point might be lowered somewhat in the case of mothers, but it would affect the results very little.) These age limits are liberal, for, it is readily seen that the grandparents of many, if not most of these children, are still living and, in some cases, are comparatively young; in like manner probably few of the parents have attained the age of 70. In some degree, liberal limits are necessary, however, because some account must be taken of the duration of the disease before death. Two sets of comparisons are shown here, namely, those based (1) on 1930 statistics applied to both parents and grandparents, and (2) on 1910 statistics applied to grandparents and 1930 statistics applied to parents. The justification for the use of the earlier statistics for the grandparents is clear.

Of the 841 diabetic children (age 15 or under at onset), seen between 1920 and 1934 and whose heredity record includes diabetic relatives reported up to May, 1935, 152 had diabetic parents or grandparents. In the great majority of these cases, only 1 of these relatives was diabetic, but in 13 cases there were 2 diabetics and in 5 cases, 3 diabetics in the direct ancestry. There were 175 diabetic parents and grandparents distributed as follows: Father, 28; mother, 21; grandfather, 53; grandmother, 73. The proportions are as follows: Diabetic fathers, 3.3%; diabetic mothers, 2.5%; diabetic grandfathers, 3.2%; and diabetic grandmothers, 4.3%.

In comparison with the 175 cases actually recorded, only 99 were expected to be diabetic on the basis of the 1930 mortality statistics and 72 where the basis for grandparents was the 1910 mortality statistics. These figures indicate an incidence of diabetes among parents and grandparents at least twice that expected in a random sample. The comparison of the ratio of actual to expected incidence as between parents and grandparents is interesting, although too much reliance cannot be placed upon it because of the relatively small number of cases involved. The excess is comparatively greatest for fathers, the actual number being over 3 times the expected. It is smallest in the case of mothers, where it is only $1\frac{1}{2}$ times the expected. Their number is low because the high maternal and fetal mortality among diabetic women almost entirely eliminates such cases except where the mother has become diabetic after the birth of the children. Among grandparents, the excess is greater for grandfathers than for grandmothers.

Mode of Inheritance. The data of this paper, therefore, support the thesis that heredity is a factor in the etiology of diabetes. The facts as recorded routinely by the senior author are typical of those found in the medical literature. As we have pointed out, the records give only the actual cases of diabetes in relatives, without sufficiently complete genealogic details to permit analysis according to genetic principles. Moreover, two circumstances have conspired to retard a correct analysis of the hereditary picture. On the one hand, certain complicating factors tend to reduce the actual incidence in families of such a disease as diabetes, and thus to obscure the relations involved. On the other hand, insufficient knowledge of the mathematical process required for the calculation of the expected number of affected (diabetic) relatives has stood in the way of the proper treatment of the problem. It is not surprising, therefore, that even among those favoring the view that susceptibility to diabetes is inherited, there has been divergence of opinion as to whether the disease is inherited as a dominant, recessive or irregularly transmitted characteristic.

The hypothesis of dominance in the transmission of diabetes is, however, untenable because on that hypothesis one would expect a far higher incidence of diabetes in the parents of diabetic children and in the children of diabetic parents than is actually recorded. To assume an irregular type of transmission would be questionable because instances of transmission of this type are rare and many of those reported are, moreover, discounted by workers in the field of heredity as either spurious or due to defective information.

The assumption of recessive inheritance in diabetes is, therefore, more logical. Allan's¹ attempt at a Mendelian analysis was unsuccessful. The genetic analysis of the more complete data, obtained by Pincus and White on cases in the present series, has yielded results that accord reasonably well with expectations. For the details the reader is referred to their original papers. It will be sufficient merely to summarize their approach and findings.

The principles involved are as follows: If the predisposition to diabetes is a recessive characteristic, persons inheriting the potentiality for developing diabetes may be designated in the usual terminology as *mm*; those not potentially diabetic but capable of transmitting the disease as *Mm* and those neither potentially diabetic nor capable of transmitting the disease as *MM*. Matings of *MM*'s with either of the other groups will produce no potentially diabetic offspring, but a certain proportion capable of transmitting the disease. The proportion varies according to whether the mating is with *Mm* or *mm*. Matings *Mm* x *Mm* produce the following proportions:

$$1MM: 2Mm: 1mm$$

Matings *Mm* x *mm* produce equal numbers of *Mm* and *mm*. Matings *mm* x *mm* produce only *mm*.

In accordance with the known facts on diabetes in the families studied, Pincus and White classified the matings as: (1) Both parents non-diabetic ($Mm \times Mm$); (2) one parent diabetic, the other non-diabetic ($mm \times Mm$); (3) both parents diabetic ($mm \times mm$). The number of families where both parents were diabetic ($mm \times mm$) was small and the results of the calculations merely suggestive. In the other 2 groups included in their first paper,^{19a} which consisted, respectively, of 440 $Mm \times Mm$ and 81 $Mm \times mm$ families, the number of children (brothers and sisters of the patient) expected to be diabetic was computed after allowing for (1) the size of the family, (2) the fact that each family was chosen because 1 member had been identified as diabetic, (3) the age incidence of onset of diabetes and (4) the fact that the expected numbers represented not actual diabetics, but persons capable of developing diabetes, and subject therefore to at least the usual mortality prior to the age at which diabetes would appear. Adjustments for these factors were made independently on the basis of several sources of data, and the results from the different bases agreed pretty well. Pincus and White found that in the group where both parents were presumably non-diabetic, 64 out of 1,495 siblings of the patients were diabetic, as compared with 64.68 expected on two different bases as regards age incidence at onset, and 68.35 on a third basis. In the families classified as matings $mm \times Mm$, there were 32 diabetic siblings out of 299, as compared with 32.43, 32.85 and 34.24, respectively, expected on each of the three bases. There were divergences in the detailed age groups of the siblings, but these need not be considered serious because of the relatively small size of the samples by age.

Pincus and White frankly recognized the weaknesses in their argument, the chief of which is that one cannot be certain that one has correctly designated the matings. Some of the non-diabetic parents classed as Mm are potentially diabetic, mm . This group includes some who have died or will have died before diabetes has developed, and it also includes living parents who may subsequently develop the disease. But computations made on the assumption of even a fairly large error in the designation of matings showed a scarcely significant deficiency of expected siblings.

Similar calculations were subsequently made by these authors²⁴ on a larger series of cases (822 families, including those of the first series) for the testing of which more carefully refined basic data were used, and further consideration was given to the error in the designation of matings. The estimates of incidence of diabetes entering into the calculations took account of the differential sex frequency, and two sets of data on age incidence at onset were used, one derived from Joslin's own cases and the other from a group of diabetics in the general population, namely, those dying in Massachusetts during the period corresponding roughly to that covered by Joslin's experience. Analyzing first the reported incidence of diabetes in the parents of this group of diabetic patients, Pincus

and White estimated that on the basis of Joslin's age at onset data, there were 158 potentially diabetic parents, of whom 146 were identified and only 12 unidentified, but that on the basis of general population age at onset data, there were 321 potentially diabetic parents, of whom 146 were identified, or a deficiency of 175 unidentified. Pincus and White next estimated the number of diabetic siblings in the families of this larger series of patients, classifying the matings according to the known incidence of diabetes in the parents, *i. e.*, no correction was made for errors in the designation of matings. In the estimates based on the Joslin age incidence, this type of error was shown to be small. The corresponding error was materially larger in the estimates based on the Massachusetts material. These estimates, in which the two bases of age at onset were used, showed the following results:

Type of mating.	Number of diabetic siblings.		
	Observed.	Expected.	
		Joslin age at onset data.	Massachusetts age at onset data.
<i>Mm</i> x <i>Mm</i>	98	121	90
<i>Mm</i> x <i>mm</i>	48	63	39
<i>mm</i> x <i>mm</i>	8	13	8

In contrast to the close agreement between the actual and the expected number of diabetic siblings in the first series, there is a sizable difference between the two sets of figures in the larger series. The material deficiency, on the basis of Joslin's age at onset data, may cast some doubt on the validity of the assumption of Mendelian recessive inheritance of the disease, but in construing these facts it must be taken into consideration that the very nature of the material makes close accounting impossible.

Thus far these analyses by Pincus and White constitute the most satisfactory approach to the problem of the inheritance of diabetes. In view of the assumption and approximations, unavoidably included in their analyses, it is probably inaccurate to say that the recessive inheritance of diabetes or of a diabetic tendency has been conclusively proved. This hypothesis of the inheritance of the susceptibility to diabetes is, however, in closer accord with the observed facts than assumptions of other types of hereditary transmission. As additional data on family histories of diabetics accumulate, it will be possible to test the theories of inheritance even more rigorously. It is hoped that other students of the subject will carefully collect and analyze series of family histories. It must be emphasized, however, that occasional and striking examples are not suitable for such analysis, but only family histories collected *seriatim*.

It should be noted in passing that Cammidge⁴ found that hyperglycemia was transmitted in mice as a recessive character.

Further evidence of the factor of inheritance in diabetes is given by Pincus and White's^{19c} study of blood sugar curves of a number of relatives of diabetics. They found that 14% of these relatives, given a routine blood sugar test, had blood sugars higher than a series of non-diabetic controls with a negative diabetic family history, and 25% of those given sugar tolerance tests gave high values, as compared with controls. The number of cases concerned was not large, but they seemed to show a distribution in accordance with the types of matings from which they sprang. Mackler and Fischer's¹³ study, however, of the blood sugars of siblings of young diabetic patients gave practically negative results. Tyner²² found that "pre-diabetes" was more frequent among those with a family history of diabetes than among those with a negative family history, the relationship being limited, however, to those where the heredity was of the direct type (*i. e.*, in parents). A large proportion of those reporting direct heredity were, moreover, obese, particularly those giving a "pre-diabetic" blood sugar curve. Not much weight, however, can be given to these findings because of the small number of cases and the general method of his study.

Summary. The influence of heredity in the etiology of diabetes is obscured by other factors, but it is unquestionably of prime importance. The percentage of patients reporting cases of diabetes in the family is notably large, even when observations are restricted to certain degrees of kinship.

Altogether 24.5% of the patients in the present series gave a positive family history. Even higher percentages were found in special groups, for example, in women as compared with men; in recent cases as against earlier cases; in diabetic children, especially the living children under observation for an extended period of time, as compared with the children who died; in physicians as compared with other patients; in Jewish patients as compared with non-Jewish patients, and in similar compared with dissimilar twins. The percentages of diabetic patients with a positive family history of diabetes are far higher than those for non-diabetic control groups. Thus, taking parents between ages 30 and 59, 8.6% of the parents of diabetics were also diabetic, compared to 0.5% of those of non-diabetics; and of the parents over 60, 9.3% of the parents of diabetics were also diabetic, but only 3.8% of the parents of non-diabetics. Similar differences were found for siblings of diabetics and non-diabetics. The incidence of diabetes in the parents and grandparents of diabetic children was found to be from approximately 2 to 2½ times the normal, according to the basis used in the estimate.

The predisposition to diabetes seems to be inherited as a Mendelian recessive character. Original work of Pincus and White on

this subject shows that the observed numbers of diabetic siblings of diabetic patients approximates, within rather close limits, the numbers expected on the basis of recessiveness. It is, therefore, concluded that the theory of recessiveness accords best with the available facts.

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THE GASTRIC JUICE IN PATIENTS WITH PERNICIOUS ANEMIA IN INDUCED REMISSION.

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THE recent advances in the physiology of hematopoiesis, especially in pernicious anemia, have emphasized the importance of the gastric secretions.^{2b,9,16,6b,11} Although it is generally accepted that the Addison-Biermer type of anemia is associated with achylia gastrica, exceptionally rare instances have been reported in the literature^{13,3,1,7,12,6a} in which "free" acid was secreted in the stomach. Further, a group of patients with a macrocytic anemia have been observed in which there has been a return of secretion of "free" hydrochloric acid after treatment with potent antipernicious anemia medication.^{17,8,4,15,14,19,10b,5,10a}

The following observations were made from data obtained from 27 patients with pernicious anemia in induced remission, who had received antipernicious anemia therapy for at least 12 months.

Methods. The patients selected were demonstrated to have pernicious anemia by their history, physical findings and laboratory procedures. The

red blood cell counts were made on a Neubauer-Levy counting chamber (new ruling, U. S. Bureau of Standards). The reticulocyte counts were made on brilliant cresyl blue stained cover slip preparations, and on each occasion 1000 red blood cells were counted.

The specimens of gastric juice were collected by continuous aspiration of the stomach for 1-hour periods by means of a water suction pump (10 cm. mercury pressure). All samples were obtained under fasting conditions (no food or fluid for at least 8 hours). Histamine stimulation was used since it is known to have no effect on gastric juice volumes in patients with pernicious anemia.^{6b} When the specimens were collected, the volume secreted per hour was determined, as well as the presence or absence of "free" hydrochloric acid. To the remaining gastric juice, sufficient concentrated hydrochloric acid was added to produce a hydrogen-ion concentration of pH 2 and the material was then stored in the ice box.

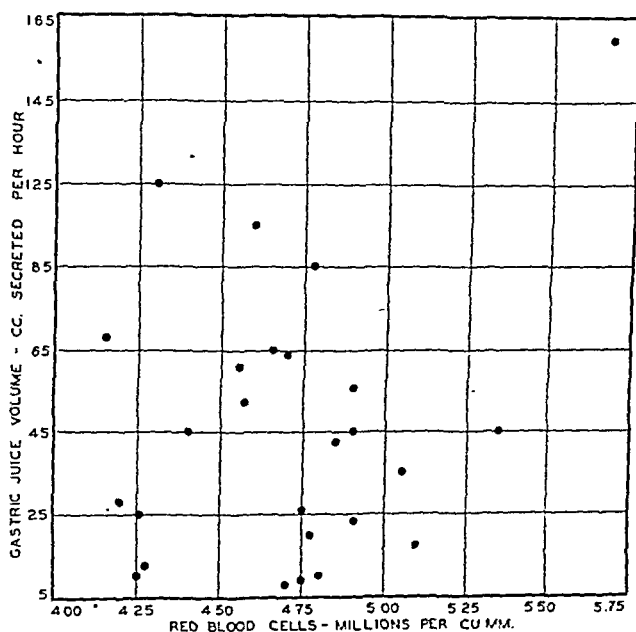


CHART I.—The relationship of gastric juice volume and peripheral red blood count in patients with pernicious anemia in induced remission.

The average gastric juice volume in the normal subject under the conditions of these observations is approximately 150 cc. per hour;¹³ in patients with pernicious anemia in relapse, 20 cc. per hour.^{6b} In individuals with pernicious anemia in induced remission, the average gastric juice volume was found to be 46 cc. per hour. The extremes of gastric secretion were 8 and 160 cc. per hour. It is to be noted that only 1 patient had a normal gastric juice volume (Table 1). From the figures plotted in Chart I, there appears to be no relationship between the amount of gastric juice secreted and the level of the peripheral red blood cell count. The latter probably is dependent upon both the amount of therapy received plus the amount of "intrinsic factor" present.^{6b} However, it is suggestive from the

figures as seen in Chart II, that a relationship exists between the individual's age and the total amount of gastric secretion. This is especially noticeable in the subjects over 50 years and those less than 50 years. It appears that younger individuals secrete more gastric juice per hour and the rate of decline of secretion is more rapid under the age of 50 years than over this age. A similar condition is noted in normal subjects.

TABLE 1.—PERNICIOUS ANEMIA IN INDUCED REMISSION.

Case No.	Red blood cells (millions per c.mm.).	Gastric juice volume (cc. per hour).	"Free" hydro- chloric acid.	Age (years).
1	4.26	25	—	53
2	4.41	45	—	52
3	4.76	26	—	56
4	4.24	10	—	70
5	4.02	40	—	63
6	4.80	10	—	64
7	4.19	28	—	68
8	4.60	95	—	41
9	5.13	17	—	69
10	5.36	45	—	56
11	4.92	45	—	43
12	5.04	35	—	67
13	4.71	64	—	39
14	4.68	8	—	68
15	4.91	56	—	45
16	4.27	13	—	50
17	4.77	20	—	62
18	4.55	61	—	45
19	4.85	42	—	54
20	5.67	160	—	40
21	4.92	23	—	66
22	4.77	85	—	57
23	4.66	65	—	65
24	4.30	125	—	61
25	4.15	68	—	47
26	4.74	9	—	54
27	4.57	52	—	46

In patients of the same age groups, the gastric juice volumes of those in therapeutically induced remission were markedly increased compared to those in relapse. In 3 of 4 cases studied in relapse and remission, there was an increase in gastric secretion from 4 to 8 fold. It is to be emphasized, however, that only in 1 instance did the volume return to the average normal level of 150 cc. per hour.

There was no "free" hydrochloric acid present in any of the specimens obtained.

The following experiment was performed to determine whether or not the "intrinsic factor" was present in the gastric contents of pernicious anemia patients in induced remission. A total of 900 cc. of gastric juice was used to make an intramuscular extract.^{9,16} This was concentrated under reduced pressure to 15 cc. Equal doses were injected intramuscularly on 3 successive days in a patient with pernicious anemia in relapse. At the onset of treatment, the red blood cell count was 1.25 million per c.mm.; the hemoglobin 31%

(Sabli), and the reticulocytes 3%. Subsequent blood changes are shown in Chart III. An initial reticulocyte increase was noted on the third day, a maximum peak of 17% on the eleventh day, and then a gradual return to the pretreatment level. This response is similar to those which were previously reported as indicative of the presence of the intrinsic factor in normal gastric juice^{2a} and in untreated patients with pernicious anemia.^{6b}

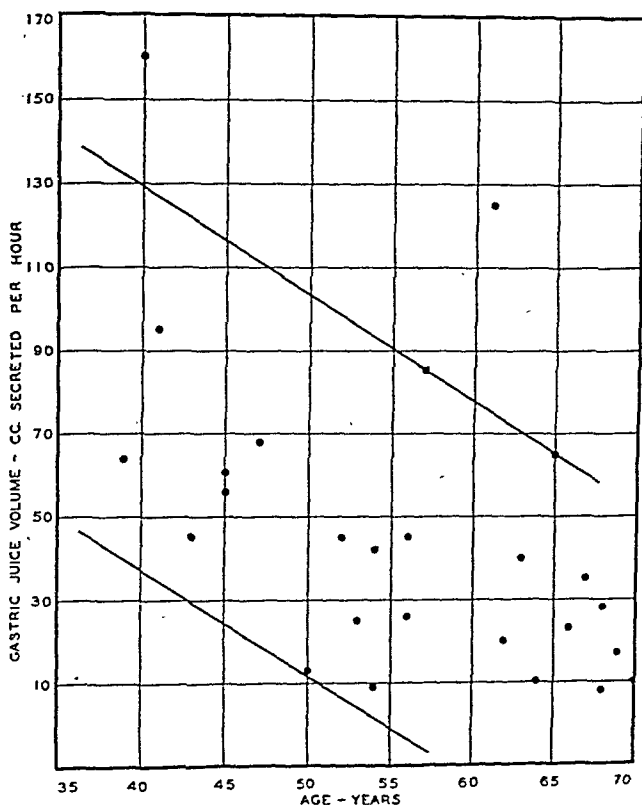


CHART II.—The relationship of gastric juice volume and age in patients with pernicious anemia in induced remission.

Discussion. Pernicious anemia is but one type of a group of macrocytic anemias, and one must of necessity rule out the various other forms such as those due to removal of the intrinsic factor or its source by mechanical means (gastrectomy), cancer of the stomach, alcoholic gastritis, failure of absorption, and failure of storage. We may then say that the macrocytic anemia of pernicious anemia results from the reduction of the "intrinsic factor" in the stomach, the exact etiology not determined. In this latter group, over 1000 gastric analyses have been performed with histamine stimulation, and without exception achlorhydria has been present.¹⁵ Twenty-

seven observations have been made on patients in induced remission with no return of "free" hydrochloric acid in the gastric contents. More than 10,000 gastric analyses have been reported in the literature and only rare cases have been noted with "free" hydrochloric acid. It would seem more likely that the macrocytic anemias observed with "free" hydrochloric acid and those with return of "free" hydrochloric acid after adequate antipernicious anemia therapy are not true pernicious anemia, but one of the other forms of disturbed hematopoiesis.

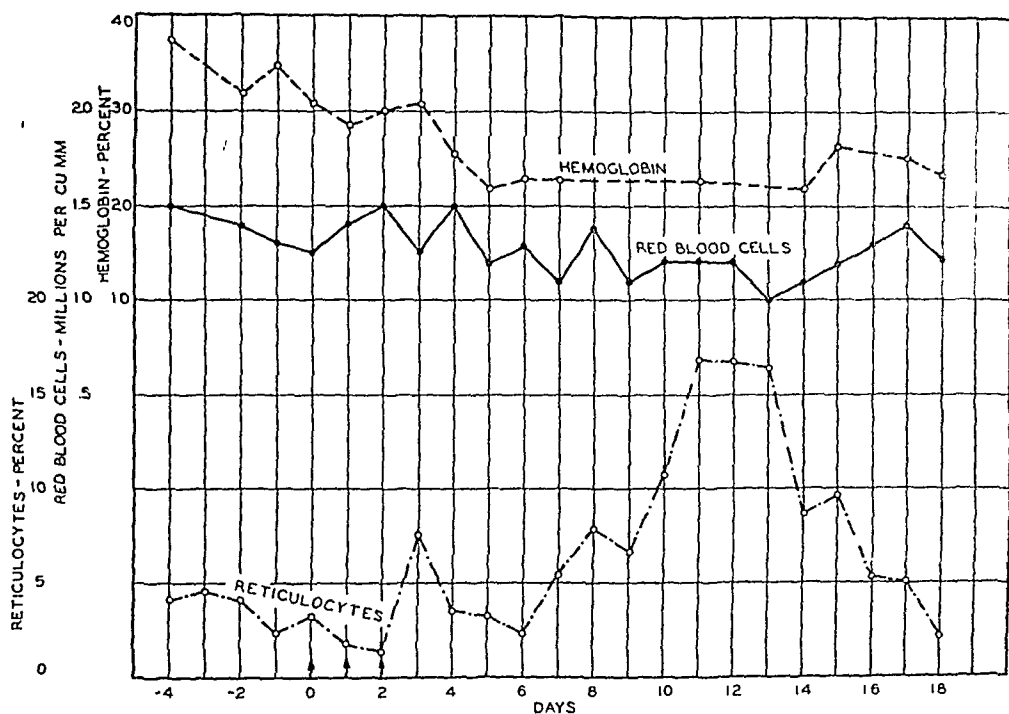


CHART III.—The effect on a case of pernicious anemia of three intramuscular injections of concentrated gastric juice obtained from patients in remission.

The decreased gastric volume observed and its correlation with age are suggestive of the fact that pernicious anemia may be due to changes resulting from early senility. The increased gastric function following antipernicious anemia therapy, casts some doubt as to the value of estimating the potency of an antipernicious anemia preparation from the maintenance dosage alone.

Conclusions. 1. The volume of gastric juice in patients with pernicious anemia in induced remission is reduced, although exceptionally it may reach the normal range.

2. The average gastric juice volume in normal subjects is 150 cc. per hour; 20 cc. in pernicious anemia in relapse and 46 cc. in pernicious anemia in induced remission.

3. No "free" hydrochloric acid was found in the gastric juice of the 27 patients with pernicious anemia in induced remission.

4. The amount of gastric secretion appeared to be related to the age of the individual, averaging 63 cc. per hour in the younger and 31 cc. per hour in the older subjects.

5. The "intrinsic factor" is present in the combined gastric juice of patients with pernicious anemia in induced remission.

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LEUKEMOID RESPONSE OF TUBERCULOUS RABBITS TO ADMINISTRATION OF TUBERCULIN.

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THE cellular changes that occur in the blood in clinical and experimental tuberculous infections have been elucidated by the studies of a large number of investigators, and, as a consequence, much information concerning the behavior of the various types of leukocytes in tuberculosis has been obtained. There have also been occasional reports in the literature of observations that suggest that, under certain conditions, individuals affected with tuberculosis may have a terminal blood picture similar to that designated by Krumbhaar¹⁰ as "leukemoid." This term denotes any condition wherein the blood picture alone (that is, without considering other diagnostic criteria) is similar to that of leukemia.

Roth¹⁶ described a case of miliary tuberculosis in which the blood picture was that of acute myelogenous leukemia; however, the morbid anatomic changes in this case failed to substantiate the blood findings. Roth also referred to 4 similar cases previously reported in the German literature. Marzullo and deVeer¹² reported

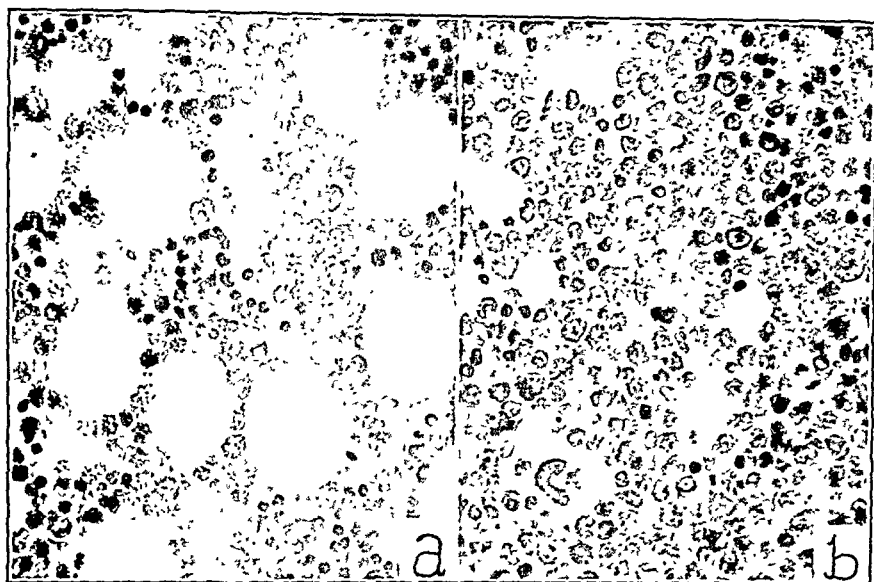


FIG. 1.—Marrow from femurs of tuberculous and non-tuberculous rabbits: *a*, normal-appearing marrow tissue; *b*, hyperplastic marrow tissue from a tuberculous rabbit 72 hours after administration of tuberculin.

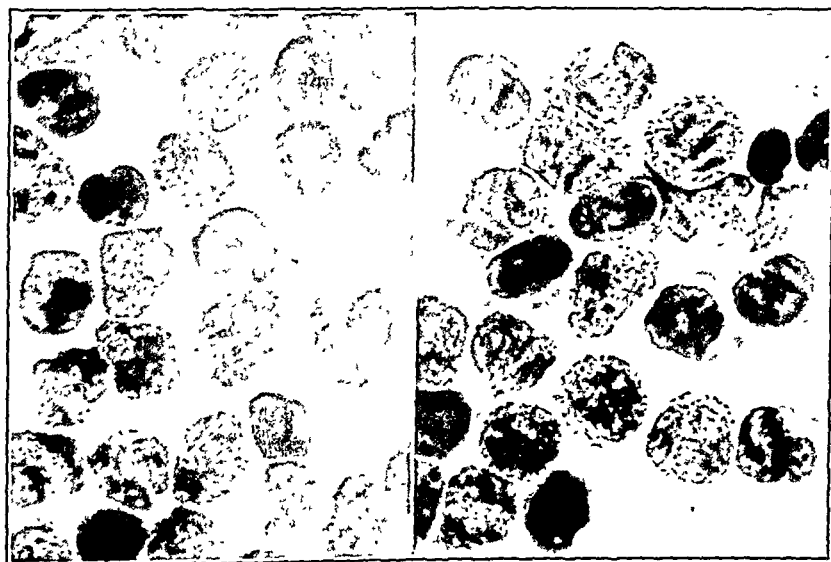


FIG. 2.—Two fields of a cover-slip preparation of the peripheral blood of a sensitized rabbit 48 hours after administration of tuberculin; immature granulocytes predominate.

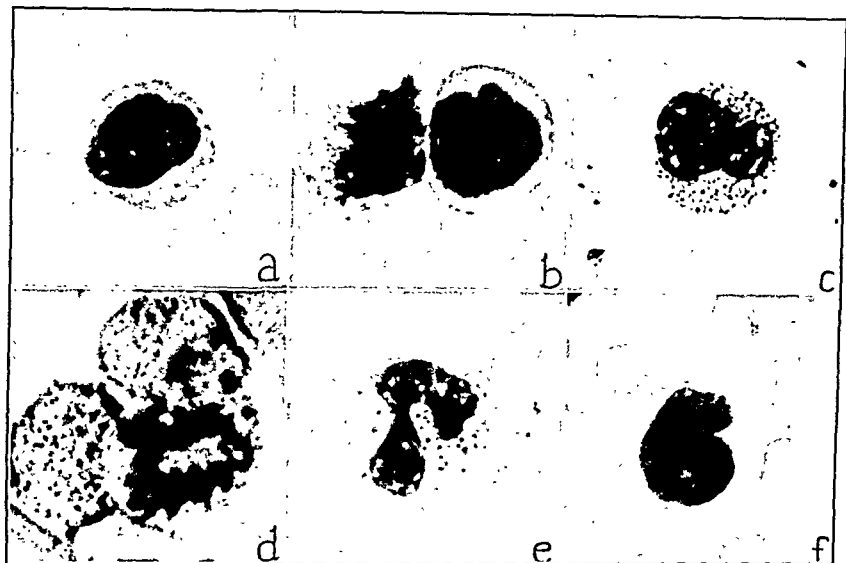


FIG. 5.—Types of leukocytes in the peripheral blood of tuberculous rabbits following injection of tuberculin: *a*, leukoblast; *b*, two promyelocytes in different phases of maturation; *c*, myelocyte; *d*, myelocyte in mitosis; *e*, late phase of metamyelocyte, and *f*, monocytic form with histocytic characteristics.

2 cases of tuberculosis, 1 pulmonary and 1 generalized, in which the blood picture was myeloleukemoid and the clinical course simulated acute myeloid leukemia. Custer and Crocker⁴ reported 2 cases in which the condition was clinically rather characteristic of myelogenous leukemia and was apparently due to widespread tuberculous infection; they concluded that "tuberculosis can produce a leukemoid blood picture of the myeloid type," and they warned against making a diagnosis of leukemia from the blood picture alone. Gosau⁵ described in detail a case of what he considered to be chronic myelogenous leukemia associated with acute septic tuberculosis. The peripheral blood picture was that of chronic leukemia of the myeloid type, but the findings at necropsy did not substantiate a diagnosis of leukemia.

From the foregoing observations on the occurrence of an excess of immature myeloid cells in tuberculous human beings, the possibility of inducing a comparable phenomenon experimentally seemed worthy of investigation. However, the explanation of the abnormal activity on the part of the hematopoietic elements of the bone marrow is not entirely obvious. Since the majority of leukemoid reactions had occurred in human beings affected with tuberculosis of rather severe proportions, a possible explanation might be the development, previously, of tuberculous allergy or sensitivity of the marrow tissues similar to that which exists in the skin of the majority of tuberculous individuals. If the myeloid tissues become sensitized to tuberculoproteins, and are suddenly brought under the influence of an excessive amount of this substance during some obscure phase in the progression of the disease, it is conceivable that the ensuing reaction could result in an excessive overstimulation of the myeloid elements.

In order to test the validity of this assumption it was decided to infect a group of animals with tuberculosis and, after sufficient time had elapsed for sensitivity to develop, to administer a rather large dose of tuberculin and then follow the peripheral blood picture and possible changes in the bone marrow.

Methods. Two groups of apparently normal adult rabbits were selected. Group 1, which consisted of 9 rabbits, was not injected with tubercle bacilli but did receive tuberculin after the normal blood picture was recorded. The amount of tuberculin given was 10 mg. per kilo. of body weight and it was administered subcutaneously. After the tuberculin was given the leukocyte picture was observed daily for four days.

Of 11 rabbits in Group 2, 9 were injected subcutaneously with a bovine strain of tubercle bacilli, 1 received avian and 1 human tubercle bacilli intravenously.* The dose given in all instances was the same: 0.5 cc. of physiologic sodium chloride solution containing the bacteria in suspension,

* Each of these bacterial strains had been previously injected into rabbits, guinea pigs and chickens and found to be typical in its pathogenicity for the bovine, avian and human varieties, respectively, of *Mycobacterium tuberculosis*. Additional observations indicate that the avian strain used is less virulent than tubercle bacilli ordinarily obtained from tuberculous chickens.

the turbidity of which being comparable to Tube 1 of the McFarland nephelometer. Following injection of the infective bacteria, the peripheral blood was examined at intervals of 1 week for a period of 4 weeks and then daily for 3 days prior to the injection of tuberculin. Tuberculin was then administered subcutaneously, the dose being 10 mg. per kilo of body weight. After the injection of tuberculin the blood was examined daily for 6 days. The animals, with the exception of 2 that died, were killed and examined for lesions of tuberculosis. Portions of the following tissues were secured at the time of necropsy for the preparation of histologic sections: liver, spleen, lungs, kidneys, skin, and bone marrow (from the femur).

In addition, portions of the bone marrow which were fixed in Helly's fluid were stained according to the method of Dominici and were examined for changes in the cellular constituents.*

Technique of Examination of Blood. Total and differential leukocyte counts were made daily between 8 and 9 A.M. The respective specimens were obtained from a freely-flowing marginal ear vein. Standard pipets were used for dilution of the blood. The cover slip and smear preparations were stained according to the May-Grünwald-Giemsa method. For differential counts, 200 cells were counted routinely and the absolute number of the different varieties per c.mm. was calculated and charted. In those instances in which a high count was obtained, the results were confirmed by examination of duplicate specimens taken at the same time.

Dry smears stained by the May-Grünwald-Giemsa technique were used and no difficulty was encountered in distinguishing between the different types of cells of the peripheral blood. As pointed out by Pappenheim,¹² the character of the nucleus and of the cytoplasmic structure is most important in distinguishing the different types of leukocytes. In reviewing the literature Hall⁷ found that the value of the supravital method in discriminating between the respective types of leukocytes is controversial; according to him the method is more useful in the study of cellular metabolism and the mechanism of phagocytosis than in distinguishing between the respective leukocytes of the peripheral blood. Hall's criticism that the effect of cellular metabolism may alter the specific distinguishing features of the monocytes warrants consideration. Extraneous factors, such as elevation of temperature and concentration of dyes as well as intrinsic physiologic change in the cell, may affect the size and pattern of neutral red bodies that constitute the characteristic rosette. For these reasons we preferred in this study to use the dry smear method.

Results. *Tuberculous Lesions in the Infected Rabbits.* All of the rabbits except one had lesions of tuberculosis at the time of necropsy; this one, in which disease could not be demonstrated either grossly or microscopically, had received the same dose of bovine tubercle bacilli as the other 8 and had been under observation for the same period. The degree of tuberculosis in the rest of the animals was with few exceptions rather limited. One of them which has been infected with the bovine tubercle bacillus and one which had been

* In addition to the rabbits just mentioned a large number of other rabbits were also injected with tubercle bacilli for the purpose of studying the leukocytic response following the administration of tuberculin. For various reasons few of these were suitable for this study. In the majority the resultant infection was either too virulent, death occurring within 3 to 4 weeks, or it was so mild that no lesions could be found at necropsy and the expected leukocytic response did not occur. Many different strains of bovine tubercle bacilli were tried before one was finally found that was satisfactory. After much experience we also found that the subcutaneous route of producing infection was superior to the intravenous one for the purposes of this study.

infected with the human form of the organism had lesions in the lung. Only 1 animal (which had been injected with the avian tubercle bacillus) had lesions in the spleen. The 8 tuberculous rabbits that had received tubercle bacilli of the bovine type all showed lesions of the subcutis in the area where the bacteria had been injected, and a few of these also had small tubercles in one kidney.*

While macroscopic tubercle-like lesions of the bone marrow were noted in but 1 animal at the time of necropsy, subsequent microscopic examination disclosed a few tuberculous foci in the myeloid tissues of 4. These lesions were characterized by an active peripheral zone of histiocytes, many of which were becoming epithelioid in character, and by central caseation in which acid-fast bacillary forms were present. Giant cells of the Langhans type were not seen, nor was there evidence of peripheral encapsulation.

Lesions of tuberculosis were observed microscopically in the kidneys of 3 rabbits. In each instance the lesions were limited to one kidney and were of an active non-encapsulated type, with caseation necrosis of the central portion in which acid-fast bacteria could be seen. Lesions of tuberculosis were present in the lungs of only two animals. These lesions were discrete tubercles, some of which were simply foci of epithelioid cells; others revealed a lymphocytic peripheral zone and central caseation (Table 1).

As has been said, tuberculous lesions occurred in the subcutis of 8 of the 9 rabbits that were injected subcutaneously with the bovine tubercle bacillus. In a few instances the lesions had ulcerated and were discharging a thin purulent exudate containing numerous acid-fast organisms. The lesions in the subcutis, while granulomatous in character, were definitely progressive. Necrosis was commonly observed in the depths of the lesion and, in a few instances, caseous cavitations had formed. The area of involvement in the subcutis of the respective animals varied in size from nodular lesions 1 cm. in diameter to flattened irregular indurated areas measuring from 4 to 5 cm. at their greatest dimension. In only one instance, Rabbit 1, was there involvement of the adjacent musculature, and in this case destruction of the muscle fibers was striking, many of the necrotic fibers containing areas of calcification. Generally speaking, however, the lesions in the subcutis were suggestive of an actively progressive and destructive type of tuberculous infection in which there was a considerable amount of necrosis and but little if any tendency toward arrestment of the disease. The extensive necrosis and ulceration noted in many of the lesions provided favorable conditions for septic complications, although the extent of the disease in most of the animals did not constitute an immediate threat to life.

* No lesion was regarded as tuberculous unless acid-fast bacillary forms were demonstrated in appropriately stained histologic sections.

TABLE 1.—EXTENT OF TUBERCULOSIS AMONG RABBITS AT THE TIME OF NECROPSY AND THE LEUKOCYTE COUNT BEFORE AND AFTER THE ADMINISTRATION OF TUBERCULIN.

Rabbit.	Type of organism.	Days under observation.*	Lesions of tuberculosis.	Degree of myeloid hyperplasia.	Leukocyte counts.†		Hours from giving of O. T. to time of maximal count.
					Average before giving of tuberculin.	Maximal after giving of tuberculin.	
1	Bovine	39	Extensive in subcutis	Well marked	21.2	81.9	24
2	Bovine	39	Subcutis	Well marked	33.0	96.0	24
3	Bovine	39	Extensive in subcutis, one kidney	Moderate	14.3	61.0	48
4	Bovine	39	Subcutis, one kidney	Well marked	13.0	115.9	48
5	Bovine	36	Subcutis	Well marked	12.3	42.0	48
6	Bovine	39	Subcutis, omentum, bone marrow	Well marked	28.2	110.0	72
7	Bovine	39	Subcutis, lungs, omentum, one kidney, bone marrow	Moderate	13.7	90.0	72
8	Bovine	39	Subcutis	Well marked	42.1	110.0	48
9	Avian	92	Spleen, portal lymph node, bone marrow	Moderate	9.9	74.0	24
10	Human	32	Lungs and bone marrow	Well marked	48.2	124.0	72

* All rabbits with the exception of Nos. 9 and 10 were killed for necropsy; Nos. 9 and 10 died.

† In thousands per cubic millimeter of blood.

NOTE: Tuberculin was administered subcutaneously to Rabbits 1 to 8 inclusive. Rabbits 9 and 10 received tuberculin intravenously.

Histopathologic Changes in the Bone Marrow and Spleen. Since Haam⁶ emphasized the fact that the bone marrow of the rabbit under normal conditions exhibits a considerable promyelocytic shift, imprint preparations alone are not suitable for the estimation of the degree of stimulation of bone marrow in rabbits. It therefore seemed more desirable to study the cellular character and density of the tissue in paraffin preparations.

The bone marrow was markedly hyperplastic, limited largely to the cells of the granulocytic series (Fig. 1). The marrow tissue was densely crowded with early myeloid cells, the majority of which were immature varieties of granulocytes. The respective types of cells could be readily distinguished in the paraffin sections by the presence of specific and characteristic granulations, and these were well defined in the Dominici preparations. Excessive stimulation of the myeloid cells had altered the normal pattern of the marrow tissue to a considerable degree. The fat tissue normally present was almost completely absent and the outlines of the sinusoids were obliterated. There was slight evidence of erythroblastic stimulation. The bone marrow therefore had responded not only by delivering into the peripheral circulation an enormously large number of

leukocytes, but actually had been stimulated to a striking degree of hyperplasia.

Myeloid cells, easily recognized by the presence of acidophilic granules in the cytoplasm, were found in the sinusoids of the spleen and occasionally in the liver. However, these cells were not in excess, and since they are known to occur under normal conditions, no significance was attached to them.

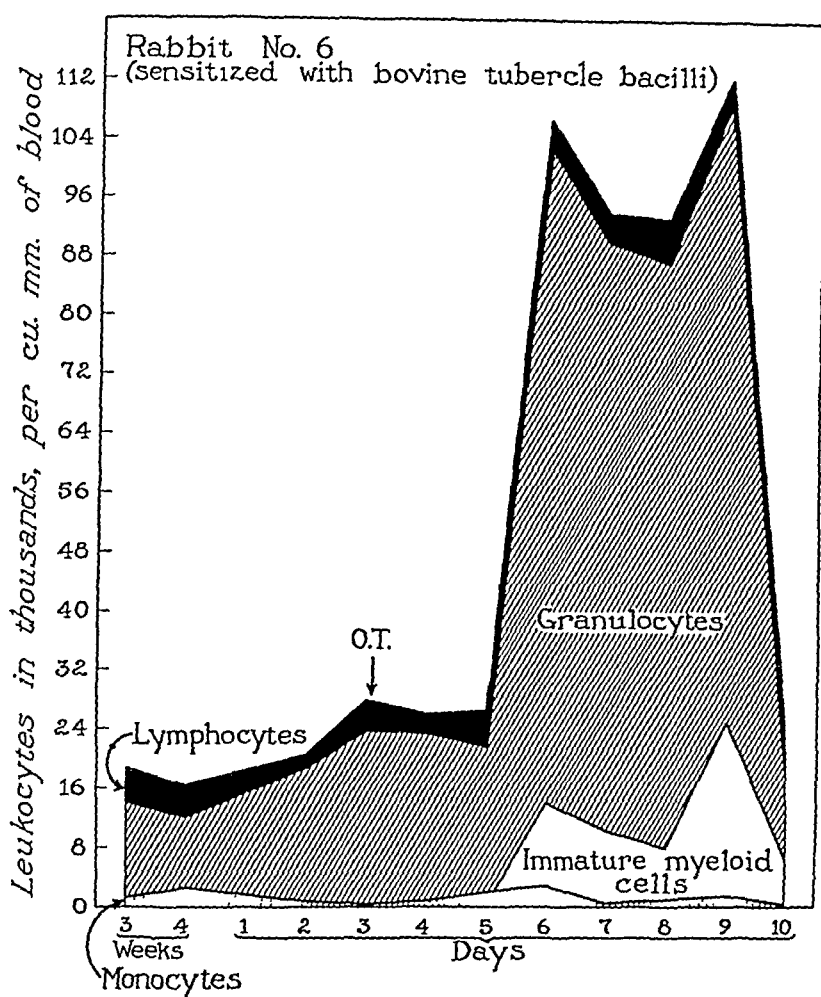


FIG. 3.—Marked increase in the total leukocyte count and the appearance of immature myeloid cells 72 hours following injection of old tuberculin. The excessive number of leukocytes disappeared after 4 days and the count returned to the level before tuberculin was given.

Quantitative Changes in the Peripheral Blood. The purpose of this particular study was to follow the changes that occurred after the administration of tuberculin to tuberculous animals. The blood picture before tuberculin was given was noted only for the purpose of establishing a base line for the estimation of qualitative and quantitative changes after the tuberculin was administered. These preliminary observations, which in most cases were made over a

period of 4 weeks after the injection of tubercle bacilli, indicate that there develops an initial, absolute and relative lymphocytosis which, during the process of the disease, tends to diminish. After the third week there is usually a fluctuation in the leukocyte count, and this is accounted for mainly by an increased number of polymorphonuclear cells in the peripheral blood. The average total leukocyte count before tuberculin was given was higher than the normal count for rabbits. The normal count of leukocytes per

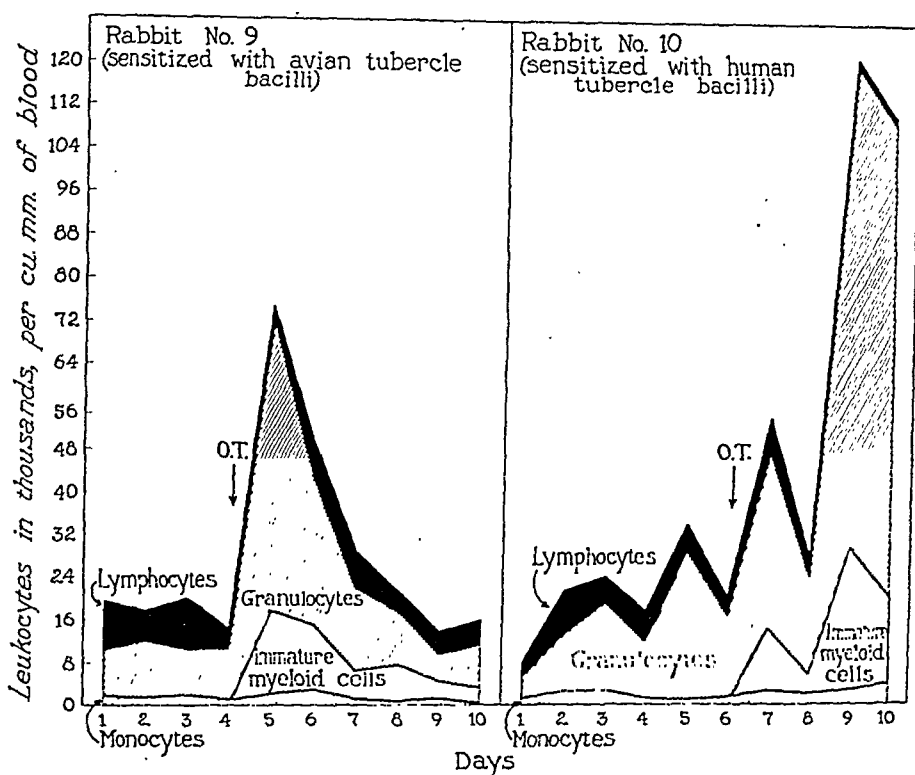


FIG. 4.—Both animals show a marked increase in the total number of leukocytes and the appearance of immature myeloid cells following injection of old tuberculin. While the total leukocyte count for Rabbit 9 was 74,000 per c.mm. of blood 24 hours after the injection of tuberculin, Rabbit 10 showed a count of 124,000 per c.mm. of blood 72 hours after tuberculin was injected.

cubic millimeter of blood for rabbits, as given by different authors, is as follows: Scarborough,¹⁸ 7900; Wirth,²¹ 8000; Haam,⁶ 10,675, and Klieneberger,⁹ 8500. Our own observations, made on 9 apparently normal rabbits, indicated the total leukocyte count to be approximately 11,000.

The most significant change following the administration of tuberculin to rabbits experimentally infected with tuberculosis was the enormous rise in the leukocyte count (Fig. 2). Twenty-four to 72

hours after the injection of tuberculin the leukocyte count of all animals showed a striking rise, and in several instances it attained a maximal increase up to 110,000 to 124,000 per c.mm. (Figs. 3 and 4). The leukocytic response, while differing in its intensity in individual animals, was always definite and of such a character as to indicate clearly an energetic stimulation of the myeloid tissues. Figures 3 and 4, which illustrate the different leukocytic reactions of 3 selected individual animals infected, respectively, with the 3 varieties of *Mycobacterium tuberculosis*, clearly indicate that a comparable reaction was manifested in each, the differences being merely quantitative.* The most impressive rise occurred in the polymorphonuclear leukocytes and, simultaneously, there was noted a marked shift to the left in these cells. Leukoblasts, promyelocytes, myelocytes, and metamyelocytes were present in the peripheral blood (Fig. 5). All three varieties of polymorphonuclear cells, the pseudo-eosinophilic, the true eosinophilic, and the basophilic, were increased. Following the administration of tuberculin the number of monocytes increased slightly, but compared to the rise in the number of polymorphonuclear cells the increase was insignificant. The number of lymphocytes showed a definite tendency to diminish.

Morphologic Characteristics of the Leukocytes. There was a marked shift to the left among the myeloid cells, and it seems desirable to give a brief description of the different types of cells observed:

Leukoblasts were characterized by blue cytoplasm and by a relatively large and round nucleus with a fine nuclear pattern, the chromatin of which was arranged in strands (Fig. 5a). The promyelocytes still retained the blue cytoplasm but the perinuclear zone showed signs of acidophilic metamorphosis. The chromatin exhibited certain degrees of condensation but retained a fine structure (Fig. 5b). Myelocytes had a round or slightly indented nucleus with well differentiated chromatin and parachromatin which often stained palely in Giemsa preparations. The special granules were relatively large in size (Fig. 5c). The metamyelocytes had definitely indented nuclei, the chromatin pattern of which, with the heavily condensed particles, resembled that of a mature granulocyte, or polymorphonuclear leukocyte (Fig. 5e). The mature polymorphonuclear cells were similar morphologically to those of human beings but differed from them in having pseudo-eosinophilic granulations. These granules took the acid dye by preference but had an affinity

* In Figures 3 and 4, which illustrate the reaction of the different varieties of leukocytes, the immature myeloid cells have been included with the total values given for the granulocytes as a group. All phases of myeloid immaturity, from the leukoblast to the metamyeloblast, were recognized. As an example of the occurrence of abnormal leukocytes, the differential count for Rabbit 9, taken at the height of the reaction following administration of tuberculin, is of interest. In this animal the different types of leukocytes were present in the following percentages: leukoblasts 2, promyelocytes 6, myelocytes 10, metamyelocytes 6, pseudo-eosinophilic granulocytes 64, basophilic granulocytes 2.5, eosinophilic granulocytes 3.5, monocytes 4 and lymphocytes 3.

to a slighter degree for basic dyes also. The true eosinophils were somewhat larger than the pseudo-eosinophils, the nuclei of the former being distinctly outlined and usually having two or three lobulations. The granules were very abundant and had a strong affinity for the acid stain.

The basophils had an indistinctly outlined, two-lobed nucleus and the cytoplasm was studded with a moderate number of deeply stained granules which varied in shape and size. The lymphocytes were round cells, with round nuclei containing markedly condensed chromatin. They were distinguished by a narrow rim of blue cytoplasm with a few large azure granules.

The monocytes were characterized by a relatively abundant light-blue foamy cytoplasm with fine azure granules. The nuclei were deeply indented or convoluted and had a very fine nuclear pattern. Often these cells were of enormous size and the cytoplasm contained varying numbers of vacuoles (Fig. 5f).

Comment. The literature on the blood picture in experimental as well as clinical tuberculosis is voluminous. There are, however, numerous conflicting data presented by different authors concerning the significance of the various types of leukocytes in this disease.

Sabin¹⁷ and her coworkers studied the changes in the blood of rabbits experimentally infected with tuberculosis using the supravital technique. They concluded that the monocyte was the cell type which is primarily affected in this disease, and they did not attach any significance to polymorphonuclear variations in the peripheral blood. Many authors who have studied the leukocyte picture in tuberculosis through the use of the dry smear method attributed to the morphologic and numerical variations of the polymorphonuclear leukocytes an important part in the tuberculous processes. Arnetz,¹ Klebs and Klebs,⁸ Miller and Reed,¹⁴ Treadgold,²⁰ Medlar and Kastlin,¹³ and many others are among those who emphasized the great importance of the variations of the polymorphonuclear leukocyte in tuberculosis.

Relatively few attempts have been made to study the changes in the blood that occur following the administration of tuberculin to tuberculous animals. Scholz¹⁹ (1912) made several observations on the hematologic changes in tuberculous calves, rabbits and guinea pigs following the injection of old tuberculin. He noted an increase in the number of leukocytes and a decrease in the number of erythrocytes. There was also a decrease in percentage of neutrophils and an increase in the percentages of the cells designated by Scholz as "lymphocytes." Since no detailed descriptions accompanied Scholz's paper, it is difficult to appraise properly the changes he reported. Wirth²¹ also referred to the observations of several authors who found that the injection of tuberculin into tuberculous animals provoked an increase in the leukocyte count. Very large doses of tuberculin resulted in leukopenia.

The injection of tuberculin into sensitized rabbits in our study instituted an enormous rise in the total leukocyte count and an absolute and relative increase in the number of polymorphonuclear leukocytes. These latter cells showed a marked shift to the left and occasional mitotic figures in the peripheral blood (Fig. 5*d*). All these features have a striking resemblance to the so-called "leukemoid" reactions described in human pathology. Experimentally, Lüdke¹¹ succeeded in obtaining a reversible leukemia-like blood picture in monkeys and dogs following the repeated injection of virulent streptococci and staphylococci after previously producing damage to the bone marrow with pyrocin. One of us (Stasney, unpublished data) obtained a leukemoid reaction in rabbits, previously sensitized with killed cultures of *Listerella monocytogenes*, following injection of a live culture of this organism.

Cases have been reported following careful study in which tuberculosis was regarded as responsible for the "leukemoid" blood picture in human beings. With this in mind the data obtained in this experimental study suggest that endogenous tuberculin-like products may occasionally stimulate the previously sensitized bone marrow to a hyperplastic condition. As a consequence, flooding of the peripheral circulation with cells of the granulocytic series ensues. Even after clinical diagnostic doses of tuberculin are given leukocytosis may occur with a shift to the left, such as was observed by Botkin,² by Arneth¹ and by Catoir.³

Some of the tuberculous animals in our series had a transitory, high leukocyte count before any tuberculin was given. Such counts, however, were never as high as those recorded after tuberculin had been administered, since following the administration of this product an enormous elevation of the leukocytic elements always occurred. These observations suggest that some toxic product liberated from tuberculous foci in the body of the rabbit may have stimulated myeloid hematopoiesis prior to the administration of tuberculin.

The maximal reaction usually followed 24 to 72 hours after the subcutaneous administration of the tuberculin; after 3 or 4 days, a sudden drop in the count was noted. This was not premortal leukocytosis, because the animals, except in two instances, lived until they were killed. Attempts were made to maintain the high leukocyte count by repeated daily administration of tuberculin; however, after 3 to 4 days the count decreased in spite of additional doses.

Summary and Conclusions. In an attempt to obtain experimentally a leukocytic response comparable to the so-called "leukemoid" reaction described as occasionally associated with tuberculosis in human beings, a group of 11 tuberculous rabbits were studied. The hematologic observations were restricted to the quantitative and qualitative characteristics of the leukocytes. The results indi-

cate quite definitely that tuberculin given to sensitized rabbits provokes an elevation of the leukocyte count, which is often of striking proportions. This increase is predominantly granulocytic and there occurs a marked shift to the left. The definite hyperplasia of the bone marrow, mitosis of the immature myeloid cells of the peripheral blood, and other significant changes suggest a condition similar to the "leukemoid" reaction. The monocytes participate in the leukocytosis rather insignificantly, whereas the lymphocytes show a definite tendency to diminish in number during the reaction that follows the administration of tuberculin. Tuberculin given to non-tuberculous rabbits has no significant effect on the leukocyte count.

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PLASMA CELL LEUKEMIA.

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THE occurrence of plasma cells in the peripheral blood has been reported in such conditions as rubella, rubeola, scarlatina,³ measles, the leukemias, Hodgkin's disease and generalized carcinomatosis. In addition a small but increasing number of cases has been presented in which circulating plasma cells have been found, not as a

secondary feature of some other main condition, but as a result of primary unrestricted hyperplasia.

The first recorded case of plasma cell leukemia which we have found was that reported by Foà in 1902,⁴ referred to as a case of pseudoleukemia plasmacellularis in which many plasma cells were found in sections of the spleen, liver and bone marrow, a few in lymph nodes and the blood. Following this, 14 other cases have been reported in which the form of plasma cell proliferation varies from myelomatous nodules in the bones accompanied by a small plasmocytosis, to massive infiltration of all organs and blood by plasma cells.

The following case is one in which all organs and the blood were diffusely involved, but without tumefaction, truly a *leukemic plasmocytosis* in the strict sense of the term.

Case Abstract. An American woman; white (N.B.), aged 66, was admitted to this hospital November 5, 1935 (service of Dr. H. W. Schaffer) complaining of weakness and a tingling sensation in her fingers. In the summer of 1935 she began to have periods of marked fatigue and nervousness; a sense of strangling and fullness of the head occurred; subsequently a tingling sensation in fingers and awkwardness of gait developed. For 6 months there had been intermittent pain in the right forearm. She went to a sanatorium where a diagnosis of pernicious anemia was made on the basis of one blood examination; intramuscular liver therapy was started, followed by some symptomatic improvement. On coming to Philadelphia in October, liver therapy was continued but symptoms, particularly those of weakness and difficulty in walking, progressed. *Past History:* Typhoid fever at 13; hemorrhoidectomy at 50; injury to spine requiring hospitalization at 50. *System History:* One attack of epistaxis the day before admission; no loss of weight; occasional dyspnea and palpitation; appetite good although diet inadequate, due to poverty. *Marital History:* Married for 13 years; divorced in 1912; two full-term pregnancies. *Physical Examination:* A well-developed, elderly woman in no distress; she is not jaundiced although skin has a yellowish tinge. There is slight exophthalmos; tongue is smooth and dry. Lungs are clear and resonant except for a few crepitant râles at left apex. Heart is of normal size with weak sounds but no murmurs. Blood pressure 112/80. Abdomen and extremities negative. Reflexes are hypoactive; sensation normal; gait awkward because of weakness. *Laboratory Tests:* Urine shows a trace of albumin and occasional leukocytes. The blood findings are reported in Table 1. Kahn test negative. Blood sugar 94 mg. %; blood urea nitrogen 17 mg. %. Gastric analysis demonstrated free acid to be present and a normal acid curve. Stool negative for parasites.

TABLE 1.—PERIPHERAL BLOOD EXAMINATIONS.

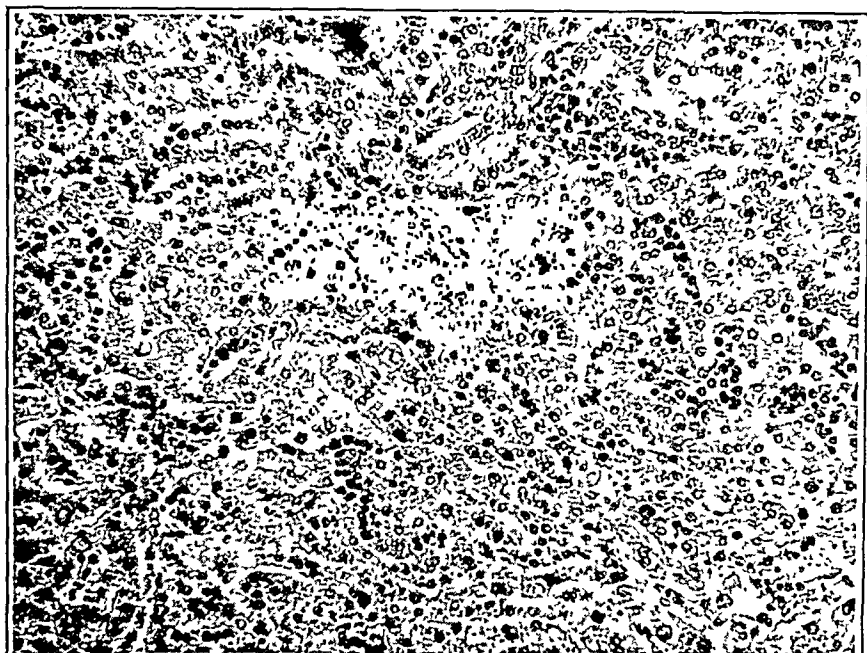
Date	Hgb. (gm.) (Haden- Hausser).	R. B. C. (mil- lions per c.mm.)	W. B. C.	Neutro- phils %	Lym- pho- cytes %	Mono- cytes %	Eosino- phils. %	Miscellaneous.
Nov. 7	9.5	2.42	7000	46	49	5	0	Poikilocytosis.
Nov. 11	9.0	2.25	5300	59	39	1	1	Anisocytosis.
Nov. 20	10.0	2.75	5200	40	48	8	4	
Dec. 3	2.57	Vol. index 1.0.
Dec. 10	10 0	2 70	Reticulocytes 0.8%

Roentgen ray of chest November 15 showed cardiac enlargement and haziness of both lung bases. Electrocardiogram showed left axis deviation with extrasystoles and depression of *S-T* intervals in Lead I. *Course:* Liver and iron therapy was begun, inducing only slight rise in number of erythrocytes and no reticulocyte response, although there was some subjective improvement. On December 11 her condition became weak with feeble pulse followed by death.

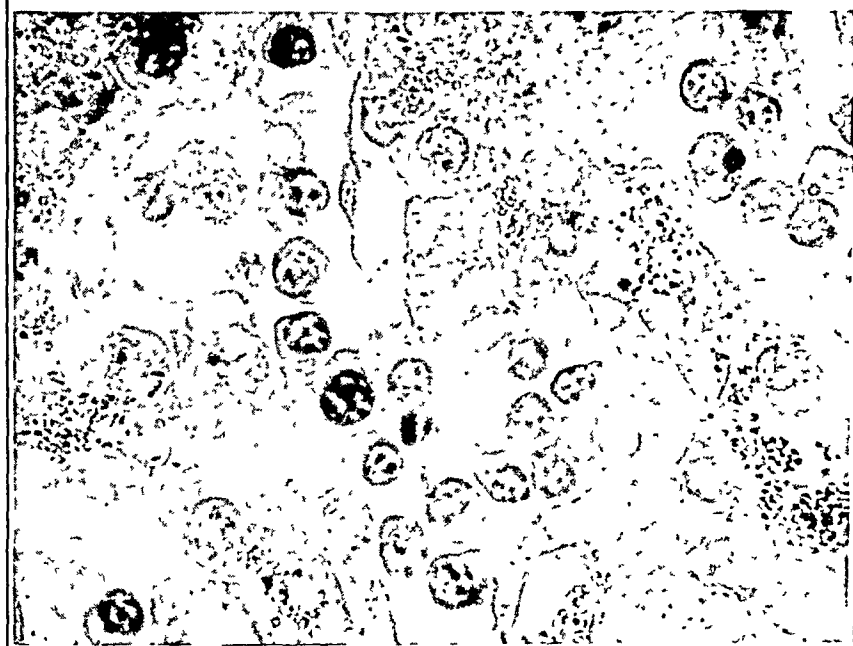
NECROPSY (P.G.H. 30486, 7 hours after death): A well developed, slightly obese, pale, elderly, white female. Skin and sclerae have slightly icteric tinge. *Heart* weighs 400 gm. Red-gray epicardium is mottled by purple petechiae. *Lungs* show congestion and atelectasis at bases. *Spleen* weighs 170 gm. and presents congested red parenchyma containing gray follicles slightly prominent for the age. *Lymph nodes* are normal in size and consistency. *Kidneys:* Each weighs 150 gm. Slightly narrowed cortices and pyramids are dotted by dark red petechiae. *Genitalia* show congestion, particularly in right broad ligament. *Gastro-intestinal tract, pancreas* and *adrenal glands* essentially normal. *Liver* weighs 1850 gm.; its softened red-brown parenchyma is congested. *Skeleton* is grossly normal; there are no tumor masses or areas of rarefaction demonstrable in vertebrae, ribs, clavicles or sternum; bone marrow is soft, moist and brown-red in color.

HISTOLOGY. In all sections taken, the blood channels, including the largest vessels and smallest capillaries, contain an increased number of leukocytes, cells of the plasmocyte series predominating. *Heart* shows marked degenerative changes and a recent thrombus in one vein. *Lungs* are atelectatic with perivascular fibrosis, marked congestion and hemolysis of erythrocytes. Vessels contain many plasma cells. *Spleen* presents marked increase in cellularity, partly due to congestion and stasis of erythrocytes and leukocytes, but more to infiltration by plasma cells, many of which are young forms. *Corpuscles of Malpighi* are well preserved. *Kidneys* show collections of plasmocytes between the tubules and in bloodvessels. In the *liver* the increased cellularity of the interstices is the most striking of all viscera. Its sinusoids and bloodvessels contain many more leukocytes than normal and here, as elsewhere, plasma cells predominate; in contrast to those in lungs, pancreas and kidney, however, many young forms (plasmoblasts) are present. Between these and the typical adult plasmocyte a gradual transition can easily be traced. *Pancreas* shows parenchymal atrophy and degeneration. *Bone marrow:* Sternum is approximately 70% cellular, well over half of the cells belonging to the plasmocyte series. There is considerable replacement of other cells by these plasma cells which number nearly 100% in some fields. Cells of the granulocyte series are present in normal proportions except for slight increase in the number of eosinophilic myelocytes; of the erythropoietic series, normoblasts predominate. Vertebral marrow is about 80% cellular; here normal hemopoietic tissue is even more extensively replaced by plasma cells. Nowhere is there any destruction of bone.

Discussion. A differential count of cells in bloodvessels of liver and pancreas (Table 2) shows approximately the same percentage of plasma cells in each although the incidence of young forms, which we have designated as plasmoblasts, is much higher in the liver. These plasmoblasts have the main characteristics of plasma cells, *i. e.*, basophilic cytoplasm with pale staining perinuclear halo and centrally or eccentrically placed nuclei in which the chromatin is arranged around the periphery in "cart wheel" pattern; but they show details indicative of immaturity such as larger size, less deeply



A



B

FIG. 1.—A, Liver showing markedly increased cellularity between cords and in periportal spaces ($\times 149$). B, Liver sinusoids crowded with plasma cells many of which are young forms (plasmoblasts) ($\times 828$).



FIG. 2.—*A*, A bloodvessel of the pancreas filled with leukocytes of which the majority are plasma cells ($\times 828$). *B*, Infiltration of bone marrow (sternum) by plasma cells and crowding out of normal marrow cells ($\times 598$). *C*, A group of plasma cells in interstices between proximal convoluted tubules of kidney. Some of these show the perinuclear halo clearly ($\times 598$).

staining cytoplasm and larger, paler nuclei with smaller and more diffusely arranged clumps of chromatin. Between plasmoblasts and adult plasmocytes, a gradual transition is readily traced.

TABLE 2.—DIFFERENTIAL COUNT OF CELLS IN VESSELS OF LIVER AND PANCREAS (H AND E AND GIEMSA STAINS.) (PER CENT). (500 CELLS EACH.)

	Liver.	Pancreas.
Plasmoblasts	36.4	5.2
Plasmocytes	35.8	68.8
Monocytes	9.2	5.8
Neutrophils	10.2	11.8
Eosinophils	0.4	0.2
Lymphocytes	1.2	1.4
Erythroblasts	1.0	0.0
Normoblasts	2.4	1.4
Unidentified	3.4	5.4
	100.0	100.0

Although no plasma cells were reported in the blood of this patient by those who studied the blood films during life, they were undoubtedly present because of their high incidence in bloodvessels of all organs examined postmortem. It is very likely that they were identified as lymphocytes which were recorded in percentages of 49, 39 and 48 in successive differential leukocyte counts.

Osgood and Hunter (1934)¹³ reported a case of plasma cell leukemia as the second in the literature. Patek and Castle (1936)¹⁴ described another case and cited 11 previously reported instances. These two recent papers have reviewed essentially the same literature, yet differ as to the number of cases which they accept as plasma cell leukemia. A study of all possible cases reveals that the distinction between the localized form of the disease (plasma cell myeloma) and the diffuse form (plasma cell leukemia) is not a sharp one and any attempted classification such as that of Piney and Riach,⁵ which considers the intermediate groups, must be arbitrary. We believe that all may be fundamentally a manifestation of the same process; nevertheless, it is obvious that some cases have certain outstanding characteristics acceptable as truly leukemic, which others lack.

An analogy may be drawn between this situation and the proliferative diseases of the lymphocyte. Corresponding to plasma cell myeloma (plasmomyeloma) are the lymphosarcomas without invasion of the blood by lymphocytes. At the other extreme, comparable to plasma cell leukemias as exemplified by the case presented, are the cases of true lymphatic leukemia. Between these two extremes, involving either plasmocyte or lymphocyte, is a group which presents a local, perhaps metastasizing tumor, from which few or many cells enter the circulating blood in leukemic fashion. The name leukosarcoma is applied to this type of case when the lymphocyte is involved; no specific term has yet been given to the plasma cell myeloma with plasmocytes in the blood. The fact that a high

percentage of the cases of plasmocytosis falls into this intermediate somewhat indefinitely demarcated group, is no doubt one of the chief reasons for the discrepancy in the number of cases accepted as true plasma cell leukemia.

Summary. An additional case of plasma cell leukemia is reported in which there was a high percentage of young plasma cells (plasmoblasts) in the liver, spleen and bone marrow.

It is suggested that plasma cell myeloma with plasmocytes in the circulating blood differs from plasma cell leukemia as leukosarcoma does from lymphatic leukemia.

* We wish to express our appreciation to Dr. R. P. Custer for invaluable assistance.

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PRELIMINARY PAIN IN CORONARY THROMBOSIS.

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THE clinical picture of coronary thrombosis is usually characterized by dramatic and sudden onset of symptoms, intractible substernal pain, dyspnea, signs of shock, sweating, collapse, nausea, vomiting and fall in blood pressure. In some cases collapse and dyspnea are present without pain, due to high pain threshold. In approximately 50% of patients the attack is preceded by angina, unrelated to effort or emotion. Fifteen such cases, the subjects of this report, were seen with substernal pain preceding the onset of the severe symptoms by hours or days. In a complete review of the literature but one reference to preliminary pain was found. Wearn² stated that "the onset may occur after a number of anginal attacks which, together with the dyspnea, may constitute the only previous warnings of involvement of the coronary arteries."

These 15 patients presented the following picture. Substernal or

epigastric (rarely precordial) pain is complained of—mild, not related to effort or emotional strain, not severe enough to confine the patient to bed and often not severe enough to lead the patient to consult a physician. This pain is more or less constant, of a burning and oppressive character and is not relieved by rest or by nitrites. The pain lasts from a few hours to 4 weeks (Table 1). If the patient has had pre-existing angina of effort and of emotion, he realizes that the attack is unlike the usual picture, that the pain is con-

TABLE 1.—ANALYSIS OF DATA.

Patient.	Age.	B. P.	History of coronary disease.	Duration of preliminary pain.	Ecg previous to attack.	Ecg during preliminary pain.	Evidence of Ecg after severe pain.	Postmortem findings.
1. H. D.*	48	134/90	48 hours	Normal	Normal	Obesity, fatty infiltration of myocardium. Recent coronary thrombosis, post. descending.
2. I. C.*	62	132/74	Angina of effort for 8½ years	24 hours	Normal			
3. E. K.	57	150/90	24 hours	Normal	Post. and basal infarct	
4. B. K.*	54	170/100	Angina of effort for 3 years	48 hours	Normal	Intraventricular block		
5. J. G.*	54	172/90	Angina of effort for 5 years	24 hours	Normal			
6. W. N.*	65	140/80	10 days	Ant. and apical infarct	Recent thrombosis ant. descending.
7. D. W.*	57	160/110	Coronary thrombosis 1½ years prev.	12 hours	Normal			
8. C. P.	58	140/90	Angina of effort for 2 years	24 hours	Normal	Previously inverted T-3 now upright. ST-4 elev. 2 mm., T-4 2.5 mm.	Ant. and apical infarct	
9. C. S.	77	184/98	Cardiac asthma 9 wks. prev. Indigestion since then	26 hours	Ant. and apical infarct	
10. F. U.	56	120/100	Angina of effort for 4 years	4 days	Post. and basal infarct. Complete A-V block	Recent thrombosis of left circumflex.
11. H. C.	54	128/80	3 weeks	Ant. and apical infarct	
12. J. J.	62	130/90	Angina of effort for 4 weeks	4 weeks	Ant. and apical infarct	Recent thrombosis of ant. descending.
13. A. S.	44	160/116	10 days (lt. elbow and scapula)	Ant. and apical infarct	
14. B. M.	54	110/70	Angina of effort for 2 months	7 days	Ant. and apical infarct	Recent thrombosis of ant. descending.
15. H. S.	51	260/160	2 years	4 days	Normal 1928	Flat. T1 and T2; elevated T3; diphasic T4	Ant. and apical infarct	

* Patient died during or soon after the onset of the severe symptoms.

stant and is not relieved by rest or the accustomed therapy. If the physician is consulted, he finds no change in the objective symptoms—the blood pressure is unaltered, and there is no fever or leukocytosis. The heart sounds are unchanged. After a variable period of preliminary pain, the clinical picture of acute coronary thrombosis suddenly makes its appearance and with it the typical electrocardiographic changes. This preliminary pain occurred in approximately 50% of the cases of coronary thrombosis observed in the past 2 years. The nature of the preliminary pains was suspected in 3 of the cases in this report.

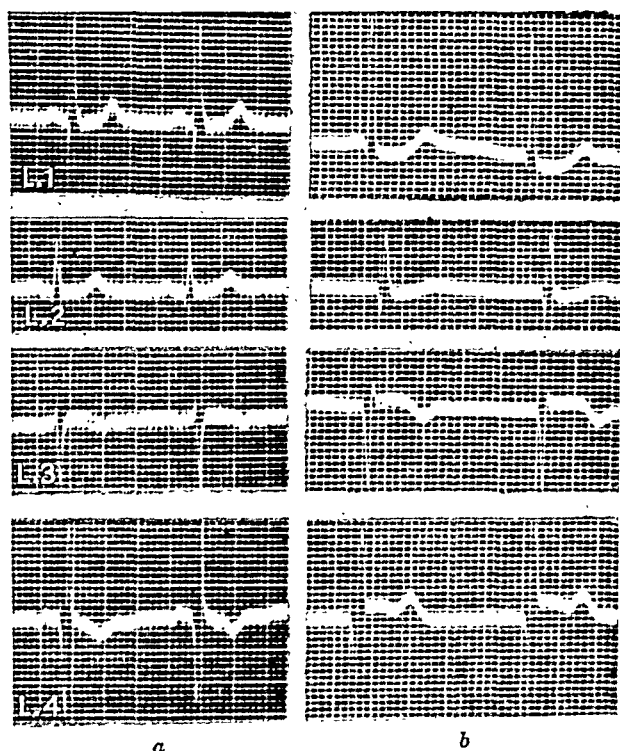


FIG. 1.—(a) Electrocardiogram of Case 3 taken during the preliminary pain (Leads I, II, III and IV). Lead IV in this and subsequent records, was taken from the apex and left leg. The record shows no abnormalities. In Fig. 1 (b), taken 24 hours later soon after the more severe symptoms, the depression of S-T and elevation of S-T in Leads III and IV with the upright T-4 confirm the diagnosis of recent myocardial infarction, involving the posterior and basal portion of the ventricles.

Electrocardiographic Observations. Electrocardiograms of 5 patients were taken during the preliminary pain. The records were normal in 2 cases (Cases 1 and 3). The changes in Cases 4, 8 and 15 are noted in the description of Figs. 1, 2 and 3.

In 4 of the 5 autopsied cases the electrocardiograms were diag-

nostic of the location of the infarcts, using the criteria of Barnes and Whitten¹ (Table 1). Death occurred during the attack of the fifth case coming to postmortem.

In Table 1 the 15 case reports are tabulated. The preliminary pain lasted from 12 hours to 4 weeks. As seen from the table, the majority of the patients had pain from 12 to 48 hours before the severe attack; 6 patients had no previous history of angina; 6 died during or soon after the attack. A previous attack of coronary thrombosis had been observed in 1 of the cases (Case 7).

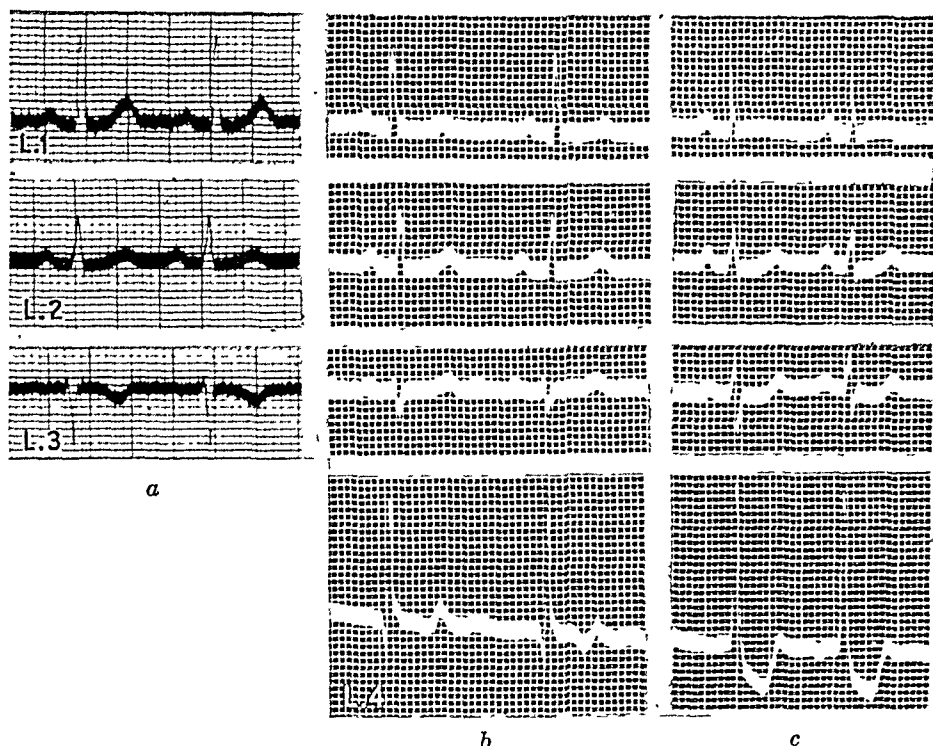


FIG. 2.—(a) Electrocardiogram of Case 8 taken 12 years before Fig. 2 (b), which was taken during the preliminary pain. In Fig. 2 (c), taken 48 hours later, slight changes of S-T have taken place in Leads I and III but the most striking is seen in Lead IV where there is a deep depression of S-T. The diagnosis of recent coronary thrombosis involving the anterior and apical portion of the left ventricle was made.

Discussion of Electrocardiographic Changes During the Preliminary Pain. A normal record, including chest leads, should not rule out a developing coronary thrombosis (Cases 1 and 3). On the other hand, slight changes in the height or contour of T in any of the leads should lend confirmation to the suspicion that change might be occurring in the coronary arteries (Cases 8 and 15). In 3 cases the curves were abnormal, but the changes were not uniform. The electrocardiographic abnormalities are probably an expression of myocardial ischemia due to coronary artery obstruction.

Pathologic Findings. The diagnosis of recent coronary thrombosis was confirmed in 5 cases by autopsy. The pathologic findings are summarized briefly.*

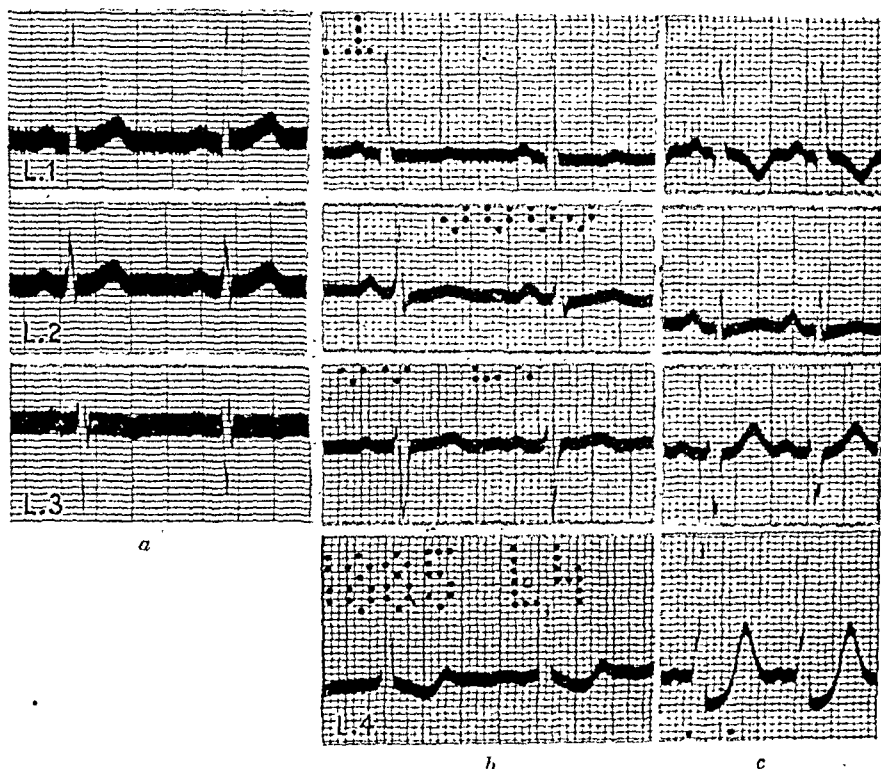


FIG. 3.—(a) Electrocardiogram of Case 15 taken 7 years before Fig. 3 (b) which was taken during the preliminary pain. In Fig. 3 (c), taken 2 days later after the characteristic clinical picture of coronary thrombosis, striking changes have occurred, elevation of S-T with depression of T-1 and low takeoff of S-T 4 with a tall peaked T-4. This record is diagnostic of a recent anterior and apical infarct.

CASE 1.—H. D. The ramus descendens anterior presented moderate atherosclerotic changes without any reduction in the lumen. The left circumflex was the seat of slight atherosclerosis. The posterior descending was severely atherosclerotic and near the apex, the lumen was greatly narrowed by atherosclerosis and was occluded by a recent thrombus. In addition, there was severe fatty infiltration of the myocardium. Of interest was the lack of myocardial infarction, the patient dying suddenly at the wheel of his car.

CASE 6.—W. N. Intimal sclerosis was present in the left coronary artery. A recent thrombus was found in the anterior descending branch, superimposed on severe intimal sclerosis. The left circumflex was small, with its entire distribution limited to the anterior and lateral portion of the left ventricle. Moderate atherosclerotic changes were present. The

* I am indebted to Dr. Alan Moritz, pathologist of Lakeside Hospital, for his analyses of the postmortem findings.

right coronary was large and the seat of extreme atherosclerosis. It supplied much of the left ventricle usually supported by the left circumflex. There was moderate reduction of the lumen of the right coronary artery just distal to its origin. A recent infarct was found involving the entire wall of the left ventricle with the anterior portion of the interventricular septum and the apex of the right ventricle anteriorly. The entire region of infarction was the seat of recent necrosis with evidence of remote infarction in the central and peripheral portions—as indicated by multiple large fibrous scars.

CASE 10.—F. U. The right coronary was congenitally small and moderately severe atherosclerosis was present. A recent thrombus was found in the left circumflex immediately distal to its origin; this artery was the seat of moderately severe atherosclerosis and there was slight reduction of its lumen. The thrombus showed evidence of organization and depigmentation. The anterior descending was moderately atherosclerotic and there was some stenosis of its lumen 2 cm. from its origin. Severe sclerosis of the intramural arteries and arterioles was present, especially in the wall of the left ventricle. Some of these vessels were occluded by recent thrombi. A large recent infarct involved the lateral portion of the left ventricle near the base and the entire posterior wall of the left ventricle. This infarct involved the entire thickness of the ventricular wall. In addition, scattered fibrous scars were present.

CASE 12.—J. J. The right coronary was almost completely occluded by atherosclerosis, a very small lumen being seen microscopically. The anterior descending was greatly reduced in lumen by atherosclerosis, and 1 cm. from its origin was completely occluded by a recent thrombus undergoing organization. A remote infarct was found on the posterior wall of the left ventricle with extreme fibrosis and aneurysmal outpouching. This infarct included the posterior part of the interventricular septum. A recent infarct was present in the anterior portion of the left ventricle (lower two-thirds).

CASE 14.—B. M. Severe occlusive atherosclerosis and recent thrombosis of the proximal portion of the anterior descending were found. In addition, the left circumflex and the right coronary were the seat of severe atherosclerosis. Evidence of remote infarction was found in the anterior and lower portion of the interventricular septum—near the apex. A massive recent infarction was found involving the tip of the right ventricle, the entire thickness of the anterior wall of the left ventricle over the lower two-thirds and the anterior and lower half of the interventricular septum.

Discussion of Pathologic Findings. Severe partially occlusive atherosclerosis was found in the thrombosed arteries in the 5 autopsied cases. In Case 1, fatty infiltration of the myocardium was present; in Case 10, numerous intramural arterial thromboses were found. In all cases but the first in this series, well defined recent infarcts were present. In 3 cases (Cases 6, 12 and 14) evidence of remote infarction was found in addition to the recent infarction. In attempting to correlate the pathologic findings with the preliminary pain, progressive reduction in the lumen—either before the formation of the thrombus or with a gradually growing thrombus, appears to be the most acceptable explanation.

Summary. Fifteen cases of coronary thrombosis and with myocardial infarction in 14, have been observed with preliminary mild anginal attacks preceding the clinical picture of thrombosis by hours or days—usually from 12 to 48 hours. This pain is not

dependent on effort or emotion, is more or less continuous and of an oppressive and burning character. The electrocardiogram was normal in 2 of 5 patients whose records were taken during this preliminary pain. The abnormal changes in the other cases are described. A gradually forming thrombus in a stenosed coronary artery appears to be the most probable explanation for the occurrence of the preliminary pain. The possibility of the development of a coronary artery thrombus should be suspected in patients who have persistent retrosternal pain, not related to effort, emotion or digestion, especially when hypertension or the anginal syndrome has been previously noted. Effort should be made to improve coronary artery flow. Urging of fluids (to avoid dehydration) administration of aminophyllin, alcohol and nitrites, moderate restriction of physical activity, mental rest, restriction of insulin and tobacco are indicated.

I wish to express my appreciation for the technical help of Helen E. Sankey, A.B., Jane Crouse and Irene McMahon.

S. A. Levine, in his recent book (*Clinical Heart Disease*, W. B. Saunders Company, Philadelphia, 1936) states that mild discomfort in the chest may precede the characteristic symptoms of coronary thrombosis by a few days.

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INFECTIONS WITH PNEUMOCOCCUS TYPE VII.*

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THE evaluation and the rational use of specific therapy in an acute infectious disease necessitates an acquaintance with the pathogenicity of the etiological agent involved. This paper deals with some

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of the more important clinical and bacteriological features of infections with the Type VII pneumococcus and particularly with the cases of pneumonia associated with this organism. In the paper that follows, the clinical and immunological observations made in the patients with pneumonia due to this type that were treated with specific serum will be presented.⁷

The Type VII pneumococcus as a cause of pneumonia ranks among the 4 most common of the types previously included in Group IV.^{2b,3,12} Of the 57 original strains found by Cooper³ to belong to this type, 2 were from the spinal fluid of cases of meningitis, 1 was from a case of respiratory infection other than pneumonia, 1 was from a normal individual, and the remaining 53 strains were from cases of pneumonia. Six of the latter were in children and 47 were in adults. At the Harlem Hospital, the incidence rate of this type has varied in different seasons from 5.5 to 8.6% of the cases of lobar pneumonia, and the fatality rates in non-serum treated cases varied from 15.0 to 31.5%.² Bullowa has presented suggestive evidence that specific serum in adequate amounts is of value in the treatment of Type VII pneumonias.² Pneumococci of this type are found only rarely as inhabitants of the nasopharynx of normal individuals.^{8,11,13}

Patients, Sources of Pneumococci and Methods. Typing sera for the newly classified types of pneumococci³ have been available at the Boston City Hospital since November 1, 1929, and have been used routinely for the serological identification of pneumococci obtained from all sources. For rapid typing, the Sabin method^{9a} and, during the past 3 years, the Neufeld method^{9b} have been used. These were checked routinely by the standard methods.¹ The typing sera for Types IV-XXXII were obtained through the courtesy of Dr. William H. Park and Miss Georgia Cooper of the Laboratories of the New York City Department of Health.

Between November 1, 1929, and June 30, 1936, Type VII pneumococci were isolated from a total of 195 cases. This represents about 5.5% of all the cases from which specifically typed pneumococci were obtained from all sources during this period. Autopsies were performed in 39 of the Type VII cases. The clinical records, roentgenograms, and autopsy protocols were all utilized and correlated with the bacteriological findings. We are especially indebted to Drs. Frederic Parker, Jr., and Robert N. Nye of the Mallory Institute of Pathology for permission to use the bacteriological and pathological data.

The conditions found to be associated with Type VII pneumococci are listed in Table 1.

Type VII Pneumococci in Conditions Other Than Pneumonia. The 29 cases of infections other than pneumonia listed in Table 1 may be considered briefly.

Focal purulent infections from which Type VII pneumococci were cultured occurred in 10 patients. Four of them had *meningitis* and all 4 died. They included: 1, a girl of 13 with physical signs of mitral stenosis but no history or physical evidence of other focal infection; 2, a man of 24 in whom an acute *ethmoiditis*, with Type

VII pneumococci cultured from the exudate, was first discovered at autopsy; 3, a woman of 64 in whom the meningitis followed an acute purulent otitis media from which a pure culture of Type VII pneumococcus was obtained; and 4, a man of 50 with a vague history suggesting a mild pulmonary infection 3 weeks prior to his admission for meningitis. The latter patient lived for several weeks in the hospital, during which time operations for cerebral abscesses were performed. There were 4 patients with *middle-ear infections*: 2 of these (both males, aged 2 and 5 years, respectively) also developed *mastoiditis* and required operation; in the third, a woman of 34, it followed a common cold; and in the fourth, a male, aged 2 years, it occurred in the course of pneumonia during which *H. influenzae* was recovered from the blood, and this organism together with *Streptococcus viridans* (but no pneumococci) were recovered from the lung at necropsy. There was 1 fatal case of general *peritonitis* in a man of 64, presumably resulting from a ruptured peptic ulcer. Finally the Type VII pneumococcus was found in pure culture in the pus from a popliteal abscess in a man of 64. This was considered to be the result of an infection within a thrombosed aneurysm.

TABLE 1.—CONDITIONS ASSOCIATED WITH PNEUMOCOCCUS TYPE VII. BOSTON CITY HOSPITAL, NOVEMBER, 1929 TO JUNE, 1936.

Disease.	All cases.		Cases with autopsy.	
	Number.	Per cent.	Number.	Per cent.
Lobar pneumonia	128*	66	21*	54
Bronchopneumonia	32	16	13	33
Empyema (on admission)	6	3	—	—
Total pneumonia and empyema	166	85	34	87
Focal infections (no pneumonia)				
Meningitis	4	..	2	
Otitis media and mastoiditis	4			
Peritonitis	1			
Abscess (popliteal region)	1			
Total focal infections	10	5	2	5
Acute respiratory infections (no pneumonia)	8			
Chronic bronchitis and bronchiectasis	4	..	1	
Chronic sinusitis	1			
Chronic pulmonary tuberculosis	3	..	1	
Total respiratory infections without pneumonia	16	8	2	5
No respiratory or focal infection	3	2	1	2
Total	195	..	39	

* Including 6 patients who had bronchopneumonia in addition.

Respiratory infections other than pneumonia were associated with Type VII pneumococci in 16 patients. With one exception, a boy

of 6 with chronic sinusitis, all were adults. Of these, 3 were females and the rest males. In 1 patient with caseous pulmonary tuberculosis and in another with chronic bronchitis, the Type VII pneumococcus was cultured from the lung at autopsy. In all the other cases, this organism was obtained from sputum. In addition to the Type VII, *Pneumococcus* Type XX was obtained from one of the patients with acute bronchitis and *Pneumococcus* Type III from a patient with tuberculosis. One of the patients with bronchitis had bronchogenic carcinoma of the lung, proved by biopsy. The patients with tuberculosis all had sputa positive for tubercle bacilli.

No respiratory or focal pneumococcic infections were demonstrated in 3 patients with the Type VII pneumococcus. These included: 1, a man of 67 with polycythemia vera and a pulmonary infarct; 2, a woman of 38 with erysipelas; and 3, a woman of 46 with pyelitis. The pneumococcus was cultured from the sputum in each of these cases.

Empyema, with pleural exudate yielding Type VII pneumococci on culture, was present in 6 patients at the time of admission to the hospital. All of these patients probably had pneumonia at home for more than 10 days previously. In each case the empyema was drained surgically soon after admission. Two of the patients, aged 3 and 7, respectively, were females; the rest were adult males, 42, 55, 59, and 77 years old, respectively, of whom 3 died. Two of the fatal cases had thin, foul-smelling, purulent pleural exudate which, in 1 case, yielded a growth of fusiform bacilli on anaërobic culture.

The Type VII *Pneumococcus* Pneumonias. The remainder of this paper will be devoted to an analysis of the 160 cases of pneumonia. These cases are all from the Medical Wards of the Boston City Hospital, to which only patients over 12 years of age are admitted. They include 30 cases treated with type-specific antibody. In the tables which follow, the latter cases will be listed apart from the patients treated without serum when such a separation seems pertinent.

Sources of the Type VII *Pneumococci* (Table 2). In a large proportion of the pneumonia cases (67, or 42%), the Type VII pneumococcus was cultured from sources which were more definitely suggestive of its etiological relationship to the pulmonary infection than its mere identification in the sputum, namely, from the infected lung, the blood, or pleural fluid. Furthermore, the same type was obtained from a second specimen, usually one or more days later, in 38 of the 93 cases in which the sputum was the only source of the pneumococcus.

Mixed Infections (Table 3). Organisms other than the Type VII pneumococcus were cultured in 22 cases (15%). Most of them were from cases of typical lobar pneumonia. They included pneumococci of other types, beta hemolytic streptococcus, streptococcus viridans, influenza bacillus, hemolytic staphylococcus aureus, and others.

TABLE 2.—SOURCES OF THE TYPE VII PNEUMOCOCCUS IN 160 CASES OF PNEUMONIA.

Source of Type VII pneumococcus.		Number of cases.	Number of specimens.
During life	Sputum	137	176
	Blood	29	44
	Exudates	8	20
	Lung	1	1
Postmortem	Heart's blood	13	13
	Lungs	28	43
	Exudates	12	14
Total number of specimens			311

Type VII pneumococci were cultured from 1 or more specimens from:

(1) Single source during life	111
(2) Multiple sources during life	17
(3) Only at autopsy	18
(4) During life and at autopsy	14

Total number of cases 160

TABLE 3.—MIXED INFECTIONS IN CASES OF PNEUMOCOCCUS TYPE VII PNEUMONIA.

Case	Lobar or "Atypical."	Termination.		Pneumococcus Type VII.		Other organisms.	Source.	Day.†
		Mode.	Day.	Source.	Day.†			
1	Lobar	Died	12	Sputum	5	Pn. (no aggl. I-XXXII)	Empyema	6
2	Atypical	Died	6	Sputum	4	Str. hem.	Blood and perit.	A
3	Lobar	Lysis	10-24	Sputum	2	Str. vir.	Blood	6 and 11
4	Lobar	Lysis	6-8	Sputum	3	Tubercle bacillus	Sputum	10+
				Blood	6			
5	Lobar	Died	8	Blood	4	Str. hem. and Staph. aur.	Lung	A
6	Lobar	Died	7	Sputum	5 and 6	Str. hem. and E. coli	Perit.	A
				Blood	6 and A			
				Lung	A			
7	Lobar	Died	9	Sputum	4	H. inf. and Staph. aur.	Lung	A
				Blood	5			
8	Both	Died	10	Blood	10 and A	H. inf.	Lung	A
				Spinal fluid	10 and A			
				Lung	A			
9	Atypical	Crisis	3	Sputum	2	H. inf.	Sputum	2
10	Atypical	Died	7	Sputum	3	Str. vir., Staph. aur. and M. catarrhalis	Lung	A
11	Lobar	Died	9	Sputum	8	Pn. IX	Sputum	8
				Lung	A	Staph. aur.	Lung	A
12	Lobar	Lysis	13	Sputum	10	Pn. III	Sputum	2
13	Lobar	Died	6	Blood	6 and A	Str. hem.	Lung	A
				Lung	A	Staph. aur.	Lung	A
14	Lobar	Died	5	Lung	A	Str. hem.	Sputum	4 and 5
							Blood, lungs and empyema	A
15	Lobar	Died	5	Lung	A	H. inf. and Staph. aur.	Lung and ethmoid	A
				Ethmoid	A			
16	Both	Died	7	Lung	A	Str. hem., H. inf. and Staph. aur.	Lung	A
17	Lobar	Died	6	Sputum	2	H. inf.	Sputum	2
18	Lobar*	Crisis	8	Sputum	4 and 7	Pn. IX	Sputum	8
						H. inf.	Sputum	4
19	Lobar*	Crisis	8	Sputum	4 and 6	Pn. IV	Sputum	6
20	Lobar*	Died	7	Sputum	2	Pn. XXI	Sputum	6
				Lung	A	Str. hem.	Sputum	6
21	Lobar*	Crisis	8	Sputum	6	Tubercle bacillus	Sputum	10+
22	Lobar*	Died	13	Sputum	7	Str. vir.	Blood	10 and A
				Lung	A	Staph. aur.	Lung	A
						Tubercle bacillus	Lung	A

* Treated with Type VII antibody.

† Day = days after onset of pneumonia.

A = autopsy.

The significance of these organisms, as noted elsewhere,⁴ varied in the different cases and could not always be evaluated from the data available.

Pneumococci other than Type VII were isolated in 6 cases. In 3 of them (Cases 12, 18, and 20), agglutinins were demonstrated for both types in the patients' serum. No Type IV agglutinins could be demonstrated in Case 19; and the Type IX pneumococcus could not be identified after careful study of the cultures made from the lungs at autopsy in Case 11. The pneumococcus obtained from the pleural fluid in Case 1 may possibly have been degraded from Type VII. *Beta hemolytic streptococci* were cultured in 7 cases. In Case 2, this organism was probably present as the original invader, the Type VII pneumococcus infection in the lung having occurred as a complication of general peritonitis present at the time of admission to the hospital. Blood culture on the fourth day was sterile in this case. In Case 14, likewise, the streptococcus was probably the original invader. In the other 5 cases, however, the data point to this organism as the cause of either a concomitant invasion or a "superinfection." *Streptococcus viridans* occurred in 3 cases. The sources of this organism and the possibility of confusing it with degraded forms of pneumococci suggest the possibility that they may have been rough variants of the pneumococcus. *Influenza bacilli* were cultured from 7 cases and were always found to be intimately related to the pneumococcus. The sources of this organism suggest it as a concomitant invader in these cases. Hemolytic strains of *Staphylococcus aureus* were usually found together with streptococci or with influenza bacilli. *Tubercle bacilli* were identified in the sputum of 3 cases in which the pneumonia occurred in the course of active pulmonary tuberculosis. There were 3 other cases, not shown in Table 3, in which hemolytic streptococci were cultured from the throat late during convalescence and were associated with acute pharyngitis or tonsillitis.

TABLE 4.—ANNUAL VARIATIONS IN INCIDENCE AND IN DEATH RATES.

Year.	Pneumococcus Type VII pneumonias.			Other cases with pneumococcus Type VII.
	Number.*	Died.	Per cent.	
1929-1930	9	4	44	5
1930-1931	18	11	67	6
1931-1932	17	2	12	3
1932-1933	19	4	21	1
1933-1934	25 ⁴	7 ⁰	28	3
1934-1935	18 ⁷	7 ¹	39	4
1935-1936	54 ¹⁹	18 ²	33	13
Total	160 ³⁰	53 ³	33	35

* The numbers include serum treated cases—the superscripts indicate the number so treated.

Annual Incidence and Death Rates (Table 4). The number of cases of Type VII pneumonia varied from year to year. If one may

judge from the small numbers here presented, the death rates also varied widely. The sharp increase in the number of cases during the last season is more than can be accounted for by the general increase in pneumococcus pneumonia during that time. Indeed, the number of cases of Type I pneumonia treated during the same period was almost the same as in the preceding years. It is of interest that during the last season the Type VII pneumococcus was also recovered from considerably more than the usual number of cases without pneumonia.

Predisposing Factors (Table 5). There were 32 cases in which the Type VII pneumonia occurred in the course of some other serious illness. In 27 (84%) of these so-called "*secondary pneumonias*" this served as a terminal event. Fifteen of these cases had "*atypical*" pulmonary lesions and constituted one-half of the cases of Type VII bronchopneumonia. The remaining 17 cases had lobar pneumonia; they represented 13% of the cases with typical lobar consolidation. The death rates among the secondary pneumonias were equally high with both types of pulmonary involvement. The nature of the "*primary*" conditions in the course of which these secondary pneumonias occurred are listed in Table 5.

TABLE 5.—SIGNIFICANT PREDISPOSING FACTORS.

		Lobar pneumonia.		Broncho-pneumonia.	
	Number of cases.	Recovered.	Died.	Recovered.	Died.
I. Primary conditions in cases of "secondary pneumonia:"					
Cardiac infarcts and decompensation	8	..	5	..	3
Hypertension (renal and cerebral complications)	4	..	1	..	3
Acute infections (peritonitis 2, active pulmonary tuberculosis 3, tuberculous meningitis 1, jugular thrombosis 1, acute encephalitis 1)	8	2	2	1	3
Acute bronchial asthma	2	1	1
Malignancy (advanced)	5	..	3	..	2
Operations (prostatectomy 1, appendectomy 1, hernia repair 1, abdominal exploration 1, excision of pituitary tumor 1)	5	1	3	..	1
Total	32	3	14	2	13
II. Other conditions not definitely related to onset of pneumonia:					
Chronic cardiac disease	5	2	2	..	1
Chronic bronchitis, asthma, and emphysema	11	4	2	1	4
Diabetes mellitus	5	3	1	1	..
Pregnancy	4	3	1
Rheumatoid arthritis	3	..	2	1	..
Severe anemia	3	2	1
Cirrhosis of liver	2	1	1
Malignancy (early)	2	..	2
III. History of alcoholism:					
Abstainers or occasional imbibers	32	21	3	6	2
Moderate chronic drinkers	9	6	3
Acutely intoxicated and/or delirium tremens	18	6	8	2	2
IV. History of antecedent upper respiratory tract infection:					
Present	57	37	10	8	2
Absent	33	26	4	2	1

Other significant conditions not directly related to the onset of the pneumonia are also listed in Table 5. They occurred with similar frequency among the cases of lobar pneumonia and broncho-

pneumonia. The death rates in these cases were lower than in the secondary pneumonias.

Acute infections of the upper respiratory tract, including colds, "grippe," and bronchitis, preceded the onset of pneumonia in 63% of the cases in which a satisfactory history was available. The cases of bronchopneumonia presenting a history of antecedent upper respiratory tract infection were "primary" pneumonias and, under these conditions, had a relatively low death rate.

A reliable history with respect to *alcoholism* was available in only a small proportion of the cases. The death rate was relatively high among the patients who were acutely intoxicated at the time of admission to the hospital and among those chronic addicts who developed delirium tremens in the course of the pneumonia. The abstainers, however, included a large percentage of young adults.

Age and Sex (Table 6). The age distribution of the cases of Type VII pneumonia was similar to that of the other common types, I, II, V, and VIII.^{5,6} The incidence among persons 70 years of age or older, however, was greater than among these types and was similar to that found among Type III pneumonias.^{6a} There was the usual predominance of males over females, the proportion being 2.3 to 1. The death rates, as usual, were higher in the older age groups. There was no difference in the death rates between the males and the females.

Bacteremia (Table 5). Type VII pneumococci were cultured from the blood in 25% of the cases of pneumonia in which blood cultures were made. The death rate in the bacteremic cases was more than 3 times as great as in the cases with sterile blood cultures. The low death rate in the cases in which no blood cultures were made is due to the fact that most of these patients were afebrile and free of symptoms very soon after admission to the hospital.

In most of the bacteremic cases in which quantitative studies with agar pour plates were attempted, these plates showed no growth and the pneumococci were grown only in the broth cultures (5 to 10 cc. of blood inoculated in 100 cc. of beef infusion broth at pH 7.8 with 0.1% dextrose added). Two non-serum treated fatal cases showed 5 and 50 colonies per cc. of blood, respectively, and 1 patient who recovered after serum treatment had 57 colonies per cc. of blood before the first dose was given. There were 6 patients treated without serum from whose blood pneumococci were grown after previous blood cultures had been sterile. Four of these patients died and one of those who recovered developed empyema. There were also 2 cases in which the initial blood cultures were sterile and subsequent ones taken just prior to serum therapy were positive. Both these patients recovered. In 3 non-serum treated fatal cases, sterile blood cultures were obtained after previous ones had yielded a growth of pneumococci.

The Pulmonary Lesion (Tables 6 and 7). One-fifth of the cases had "atypical" consolidation of the lungs and are included under the term "bronchopneumonia." There were also 6 fatal cases in which typical lobar pneumonia was present in part of the lung and, in addition, atypical consolidation was found at autopsy in other lobes. The death rate was considerably higher among the cases of bronchopneumonia than in those with lobar pneumonia, due to the large proportion of secondary pneumonias among the former. The extent of the pulmonary involvement is shown in Table 7.

TABLE 6.—ANALYSIS OF INCIDENCE AND DEATH RATES.

TREATMENT OF PNEUMONIA AND BRONCHOPNEUMONIA.									
			Treated without serum.			Treated with serum.			
	Number.	Per cent incidence.	Number.	Died.	Per cent.	Number.	Died.	Per cent.	
All cases	160	100	130	50	38	30	3	10	
Age (years)	12-19.	15	9	12	0	3	0		
	20-29.	31	19	21	5	10	0		
	30-39.	30	19	24	3	6	2		
	40-49.	29	18	22	11	7	0		
	50-59.	26	16	24	11	2	0		
	60-69.	13	8	11	6	2	1		
	70+	16	10	16	14	0	0		
Sex	Males	112	70	93	35	38	19	2	11
	Females	48	30	37	15	41	11	1	9
Blood culture	Positive	35	25	30	27	90	5	1	20
	Negative	105	75	80	21	26	25	2	8
	Not done	20		20	2	10			
Lobar pneumonia	128*	80	100	33*	33	28	2	7	
Bronchopneumonia	32	20	30	17	77	2	1	50	

* Including 6 cases with atypical consolidation in other parts of the lung.

TABLE 7.—EXTENT OF PULMONARY INVOLVEMENT.

Lung involvement.	Treated without serum.		Serum treated.	
	Recovered.	Died.	Recovered.	Died.
Lobar pneumonia:				
1 lobe	43	13	22	
2 lobes, unilateral	14	7		
2 lobes, bilateral	4	3	3	
3 lobes, unilateral	5	4	1	1
3 lobes, bilateral	1	2*	..	1
4 or 5 lobes	4*		
Bronchopneumonia:				
Mostly unilateral	5	5	..	1
Bilateral	8	12	1	

* These cases all had atypical consolidation in part of the involved lung.

Diagnostic Symptoms (Table 8). The symptoms of pneumonia due to the Type VII pneumococcus were similar to those due to other types. The characteristic symptoms were elicited more regularly in the cases with typical lobar pneumonia than in those with bronchopneumonia. In the table is noted the frequency with which each of the more important of these symptoms, which are so often helpful in the early diagnosis of pneumonia, were encountered in the present series of cases.

TABLE 8.—COMMON DIAGNOSTIC SYMPTOMS.

	Lobar pneumonia (119 cases with reliable history). Per cent of cases.	Bronchopneumonia (24 cases with reliable history). Per cent of cases.
Onset: Sudden	87	79
Gradual	13	21
Diagnostic features:		
One or more chills	75	67
Pleuritic pain	96	79
Bloody or "rusty" sputum	64	38
All 3	52	21
Only 2	31	46
Only 1	14	25
None	3	8

TABLE 9.—DURATION OF ACUTE ILLNESS.

Day of lysis, crisis or death.	Cases treated without serum.		Serum treated cases.	
	Recovered.	Died.	Recovered.	Died.
2	1	1	2	
3	4	1	2	
4	3	1	5	
5	4	4	8	
6	6	4	5	
7	13	6	1	
8	18	3	3	1
9	11	3	1	
10	8	1		
11	3	..		1
12	5	1		
13		1
14	4		
15-21	1	4		
21+	2	7		
Not known	1	10		
Total	80	50	27	3

TABLE 10.—COMPLICATIONS OF PNEUMONIA (160 CASES).

Complication.	Number of cases.		
	Recovered.	Died.	Autopsied.
Empyema	3	6	6
Pericarditis	5	5
Meningitis	3	3
Endocarditis	3	2
Otitis media and mastoiditis	1	1	1
Subcutaneous abscess	1		
Pulmonary abscess	1	1
Phlebitis (saphenous)	1		
Pulmonary infarct	1	1
Acute tracheobronchitis	?	15	15
Sterile pleural effusion	4	8	8
Jaundice	3	1	1
Massive atelectasis	3	2	2
Focal liver necrosis	0	1	1

Duration of Acute Illness (Table 9). In about two-thirds of the recovered non-serum treated cases, crisis or lysis took place between the seventh and the ninth day after the onset of the pneumonia. Only 22% of these cases had crisis or lysis before the end of the sixth day. Among the serum treated cases, on the other hand, crisis or lysis occurred on or before the sixth day in 84% of those who re-

covered. In the fatal cases, death occurred most commonly between the fifth and ninth days, but a large number of cases died after an illness of 2 weeks or more. Death occurring before the fifth day was uncommon.

Complications (Table 10). Focal purulent complications were relatively infrequent and were often first discovered at autopsy. One case of "pleural eosinophilia," reported elsewhere,¹⁰ is included among the recovered cases of sterile pleural effusion.

Discussion. It has been shown that, for the most part, the Type VII pneumococcus is associated with acute pneumonia. It may, however, give rise to focal infections without preceding pneumonia. Also, in a small percentage of the cases from which this organism was cultured, there was a simple infection of the upper respiratory tract or bronchitis without pneumonia. Whether this organism is etiologically related to these infections as a primary or secondary invader, or whether it merely multiplies so that it can be isolated in cultures during infections with other living agents, cannot be determined from the data at hand.

About one-fifth of the cases of *Pneumococcus* Type VII pneumonia were found to be bronchopneumonias with "atypical" pulmonary lesions and frequently with less typical symptoms than in the cases with classical lobar pneumonias. To be sure, many of these "atypical" cases were secondary to other serious illness, and the death rate was accordingly high; one-half, however, were apparently "primary" pneumonias, except for antecedent simple infections of the upper respiratory tract, and were associated with a similar death rate to that found in the cases of lobar pneumonia due to this type.

There are no data available, as yet, with respect to the benefit that may be derived from specific serum therapy in cases of atypical pneumonia. It is essential, however, as specific serums for the newer types become available, to bear in mind the possibility that some primary pneumococcus pneumonias may have atypical symptoms and pulmonary lesions. This has been found to be true for cases of this type and also for Type V cases.⁵ It thus becomes important to "type" all early cases of acute pulmonary infection, instead of reserving this procedure for only those cases presenting the classical symptoms of typical lobar pneumonia. Limitation of typing to such cases was justifiable where useful specific serums were limited to the Type I and Type II pneumonias which are almost always typical lobar pneumonias.^{5,6}

In the present paper, the question of the efficacy of specific serum therapy was touched upon only in the tables dealing with death rates and duration of illness. These data, alone, although based on only a small number of treated cases, suggest that specific treatment may be useful in reducing the death rate and in curtailing the course of the acute illness in cases of pneumonia due to this type. Serum therapy, in these cases, will be considered in more detail in the paper which follows.⁷

Summary. The salient clinical and bacteriological findings in 195 cases in which the Type VII pneumococcus was cultured have been presented. In particular, the findings in 160 cases of pneumonia associated with the Type VII pneumococcus were presented. These included 30 cases of bronchopneumonia. In the cases treated with specific serum, 30 in number, all but 2 of which were cases of typical lobar pneumonia, the death rate was appreciably lower than in the cases not treated with serum, and the duration of the acute illness was apparently curtailed.

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CLINICAL AND IMMUNOLOGICAL OBSERVATIONS IN CASES OF PNEUMOCOCCUS TYPE VII PNEUMONIA TREATED WITH CONCENTRATED TYPE-SPECIFIC ANTIBODY.*

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THE preceding paper⁷ presents the more important clinical and bacteriological findings in 160 cases of Pneumococcus Type VII pneumonia, including 30 cases in which specific serum therapy was

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used. The data indicated that in this small group of serum-treated cases the death rate was lower and the acute disease was shorter than in comparable cases treated without serum. The present paper is concerned more particularly with the clinical course and the serological features of the 30 serum treated cases.

Patients, Materials and Methods. In general, the criteria used in choosing cases for specific treatment with Type VII antibody, the bacteriological and serological methods, the therapeutic serum, and the method of its administration were similar to those employed in the study of specific therapy in Type V pneumonia.⁵ The Type VII antibody was available at different times between February, 1934, and June, 1936. It was prepared, concentrated, and supplied by the Lederle Laboratories, Inc. Different lots varied in potency from 4000 to 6000 units per cc., the unit being defined as the equivalent of 1/300 cc. of a standard serum, L1. The earlier lots were polyvalent, containing antibodies in comparatively low titer for Types IV, V, and VIII, and the later lots bivalent, with only Type V antibodies in addition to those for the Type VII pneumococcus. In 23 of the cases, treatment with serum was begun within 96 hours of the onset, in 4 (Cases 5, 9, 22, and 28) the first dose was given early in the fifth day and in the 3 remaining cases it was first given on or after the sixth day. During the first 2 seasons, the total initial dose was usually about 200,000 units given in 3 injections within a period of 4 hours. This was reduced during the last season to between 60,000 and 100,000 units, as in the Type V cases.⁵ Additional doses were given, when available, for bacteremia and when the clinical response to the initial dose was not entirely satisfactory. The Type VII pneumococcus used in the serological tests was one of the original Cooper strains. This was kept at maximum virulence by daily mouse passage throughout this study.

Clinical Results. *Death rates* among the serum-treated cases were lower than among the cases treated without serum when compared in different seasons, according to age, sex, and the presence or absence of bacteremia and with respect to the extent of the pulmonary lesion. These comparisons are shown in Tables 4, 6, and 7, respec-

EXPLANATION OF THE CHARTS.

Typical lobar pneumonia was present in almost every instance. The lobes involved when treatment was begun are indicated in the upper left corner. RLL = right lower lobe; RUL = right upper lobe; LLL = left lower lobe, etc. The cases in which the pulmonary consolidation was "atypical" are designated as bronchopneumonia.

The age of the patient is given in the upper right hand corner between the initials and sex designation and the hospital number.

Type VII pneumococci were obtained from the sputum, usually on more than one occasion, in every case of Type VII pneumonia. These results are not shown in the charts unless especially indicated.

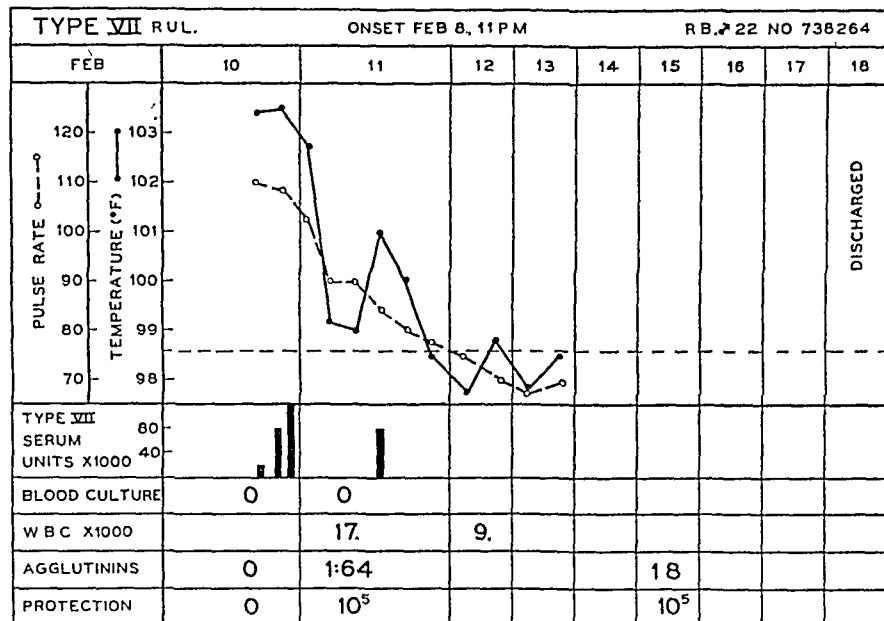
Blood cultures: 0 = sterile; + = positive for Type VII pneumococci.

Agglutinins: 1:2, 1:4, etc. = the highest dilution of serum in which floccular agglutination of Type V pneumococci was observed. + or ± = moderate or slight clumping of Type V pneumococci seen microscopically in a serum in which agglutinins could not be demonstrated macroscopically.

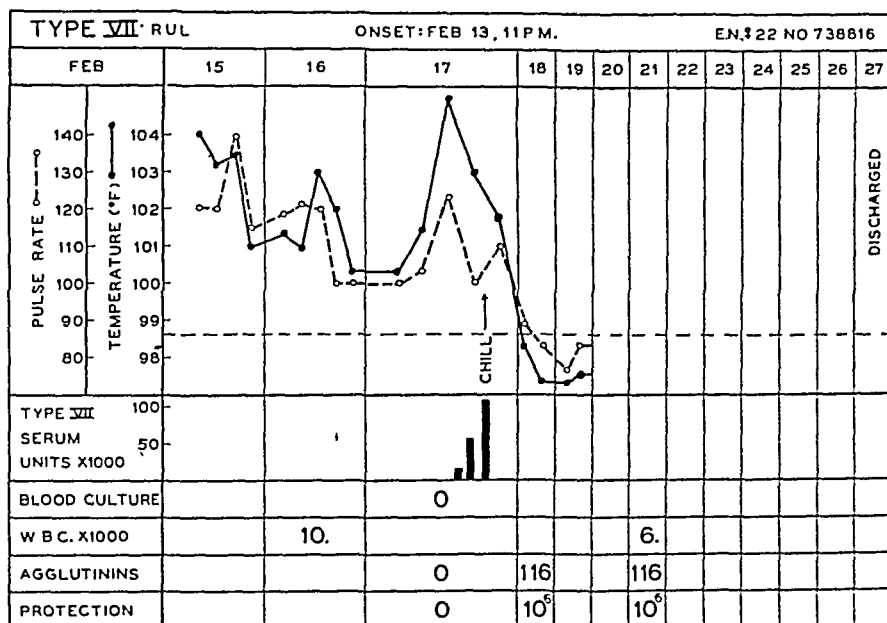
Protection: 0, 10⁵, 10³, etc. = the largest number of fatal doses of pneumococci against which mice were protected by 0.2 cc. of serum.

PN = pneumococcus; the type is designated by Roman numerals.

tively of the previous paper.⁷ Although the reduction in the death rate was striking, it can not be considered as conclusive evidence of



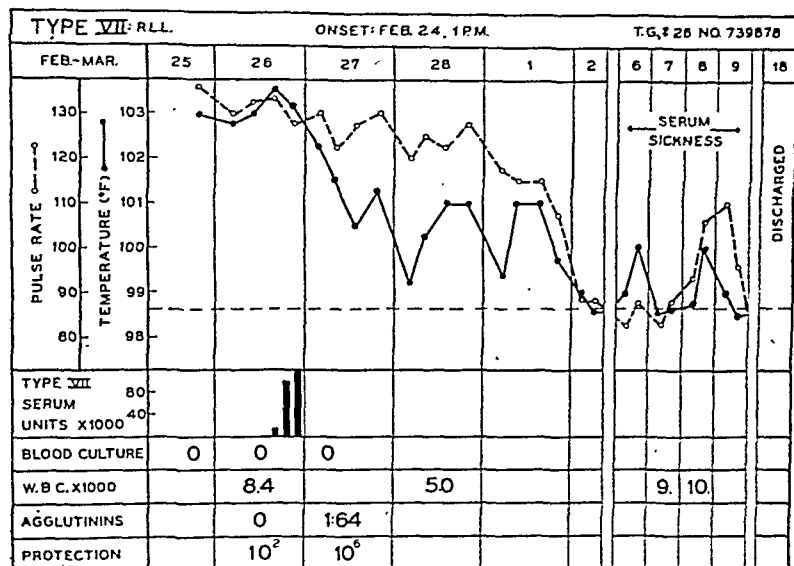
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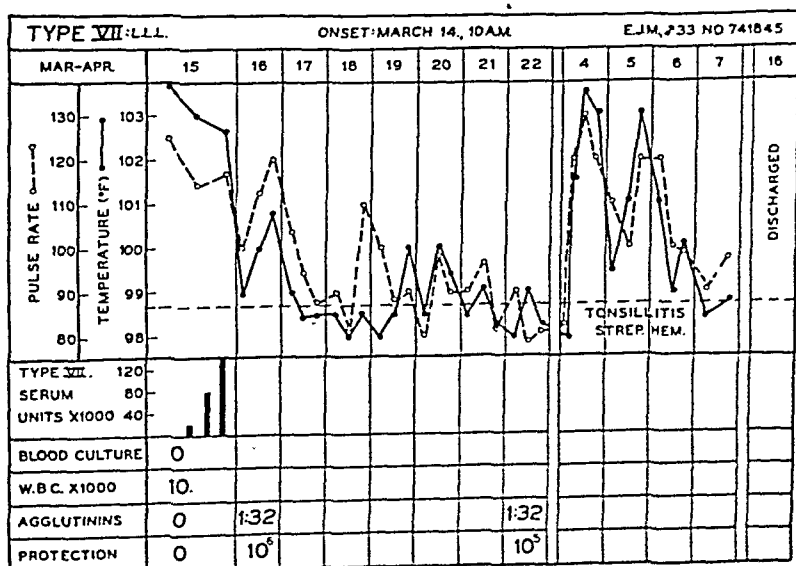
CASE 2.

the efficacy of specific antibody because of the small number of cases and the possible objections to the selection of cases for treatment.

Effect of Serum on the Acute Disease. It was our purpose here, as in the studies on therapy in pneumococcus pneumonia of other



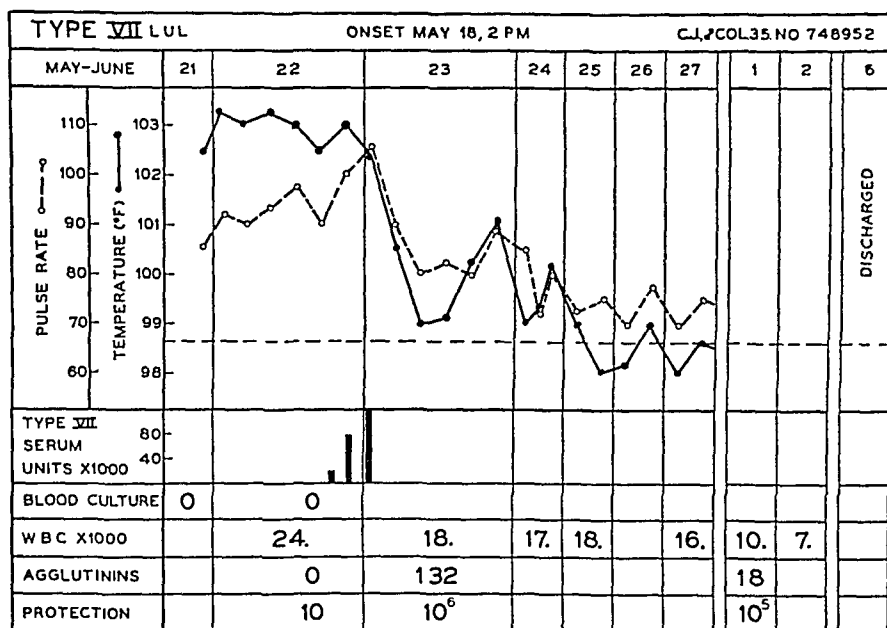
CASE 3.



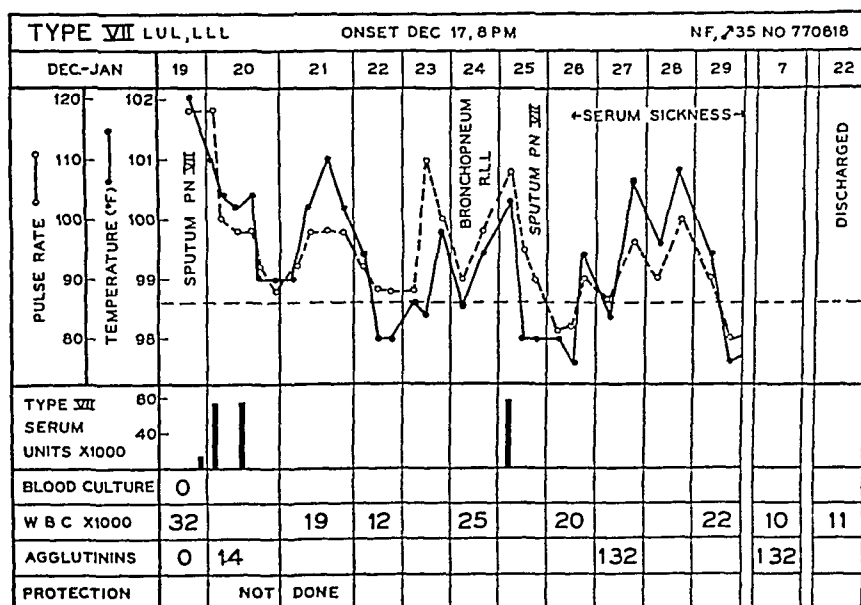
CASE 4.

types, ^{2,3,5} to observe the effect of serum therapy on the course of the disease in each patient. The uniformity with which rapid clinical improvement could be correlated with the administration of

serum would then help not only to evaluate the efficacy of this agent, but also, possibly, to define the limits of its usefulness. Accordingly,



CASE 5.



CASE 6.

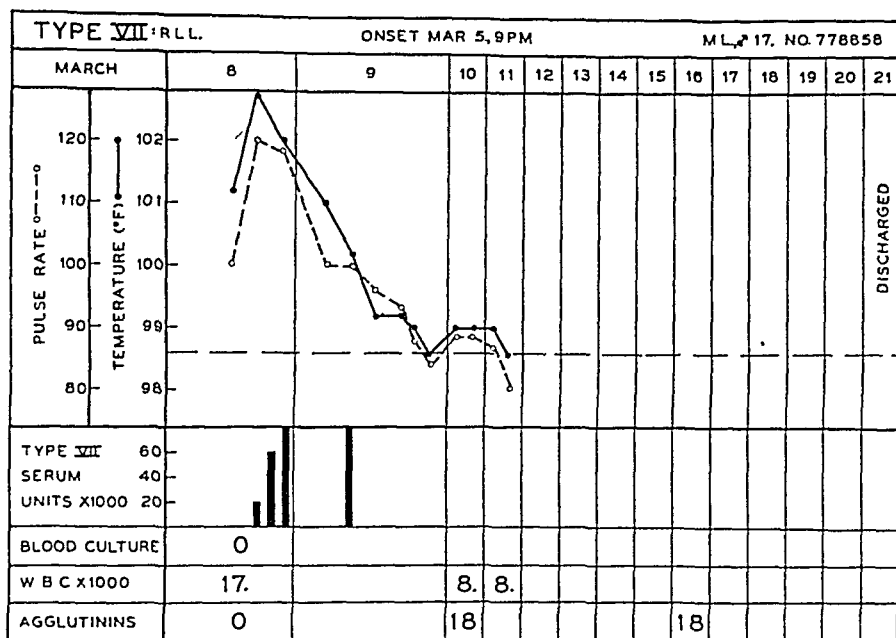
we shall note, first, the effect of the specific antibody on the course of the disease in general and then, more particularly, the cases which may be considered therapeutic failures, namely, the fatal

cases and those in which recovery occurred apparently without relation to the antibody administration.

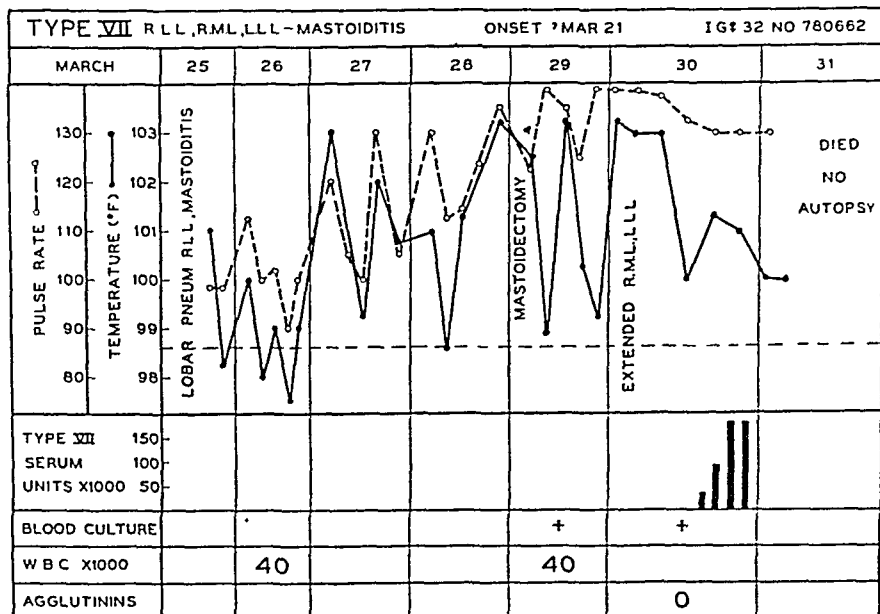
The influence of specific serum therapy on the acute disease is best reflected in the accompanying charts which show, for each case, the relationship between the antibody administration and the fever and pulse rate. The total duration of symptoms referable to the pneumonia, that is, to the time of crisis, lysis, or death, was noted in Table 9 of the previous paper⁷ for both the serum treated cases and for those not receiving serum. The average duration of illness at the time of the first injection of serum was 76 hours, judging from the time of the initial chill or pleuritic pain. Of the 27 patients who recovered 18 were free of fever, elevated pulse rate, dyspnea, and prostration within 24 hours after serum treatment was begun. The fatal cases and those in whom fever and symptoms persisted longer than 24 hours after beginning serum treatment may be considered briefly.

Fatal Cases. In Case 8, the illness began with an acute otitis media, and incision of the tympanic membrane for drainage was done 2 weeks before admission to the hospital. This operation gave only partial relief. Four days before entry, the patient experienced chills, fever, and pain in the right chest. At the time of admission there was clinical and Roentgen ray evidence of mastoiditis and also of pneumonia of the right lower lobe. Simple mastoidectomy was performed under nitrous-oxide and oxygen anesthesia, supplemented by ether. The jugular sinus appeared to be normal at the time of operation. The condition of the patient became worse, the pneumonia extended to the right middle and left lower lobes, and the blood culture, taken several hours after the operation, was positive for Type VII pneumococcus. Treatment with specific antibody was undertaken when the result of this culture became known, namely, on the tenth day of the pneumonia. The patient, at this time, was failing rapidly. A total of 480,000 units were injected within 6 hours without untoward reactions. There was no improvement in the patient's condition and she died 10 hours after the last injection. A lumbar puncture done for symptoms of meningitis before serum treatment was begun yielded normal spinal fluid. In Case 24, no improvement followed treatment with a total of 260,000 units given over a period of 55 hours. Type XXI pneumococci and beta hemolytic streptococci were recovered from the sputum on the day before death. Cultures made from the lungs at autopsy, 18 hours after death, yielded Type VII pneumococci, hemolytic streptococcus, and Staphylococcus and Streptococcus viridans, but Type XXI pneumococci could not be isolated. The history in Case 29 was not reliable due to the presence of active delirium tremens and some language difficulties. As far as could be ascertained, the acute illness was of 6 days' duration at the time of admission. Specific serum was given promptly after Type VII

pneumococcus was obtained from the sputum, but no improvement in the patient's condition followed. Blood cultures taken before



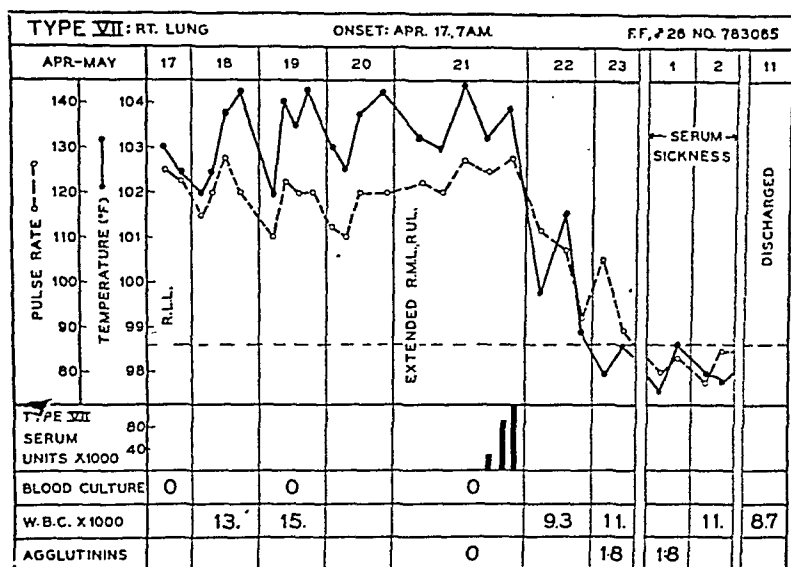
CASE 7.



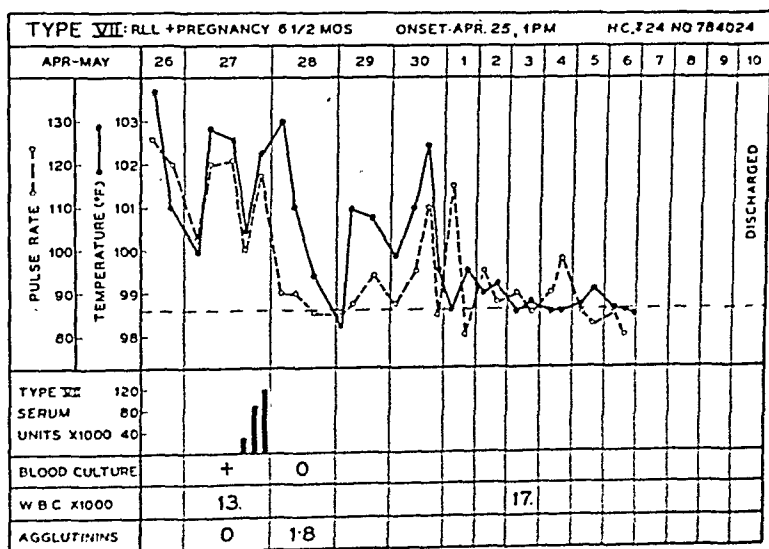
CASE 8.

serum therapy remained sterile, but one taken 3 days later and another taken at autopsy yielded an organism having most of the characteristics of *Streptococcus viridans*. Autopsy revealed a fibro-

caseous tuberculosis of both lungs. Tubercle bacilli were demonstrated in a smear of the exudate from one of the lungs. Other details in these cases are noted in the charts.



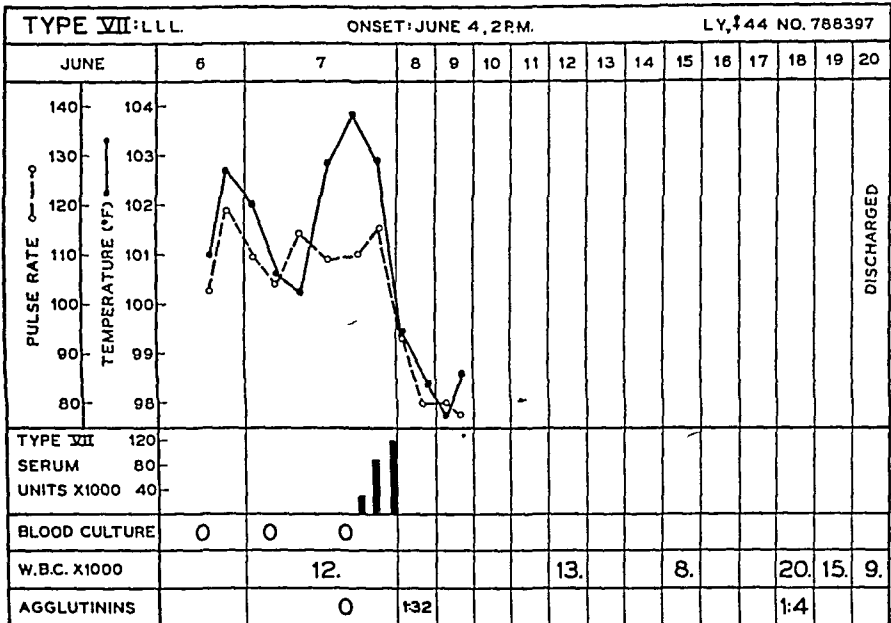
CASE 9.



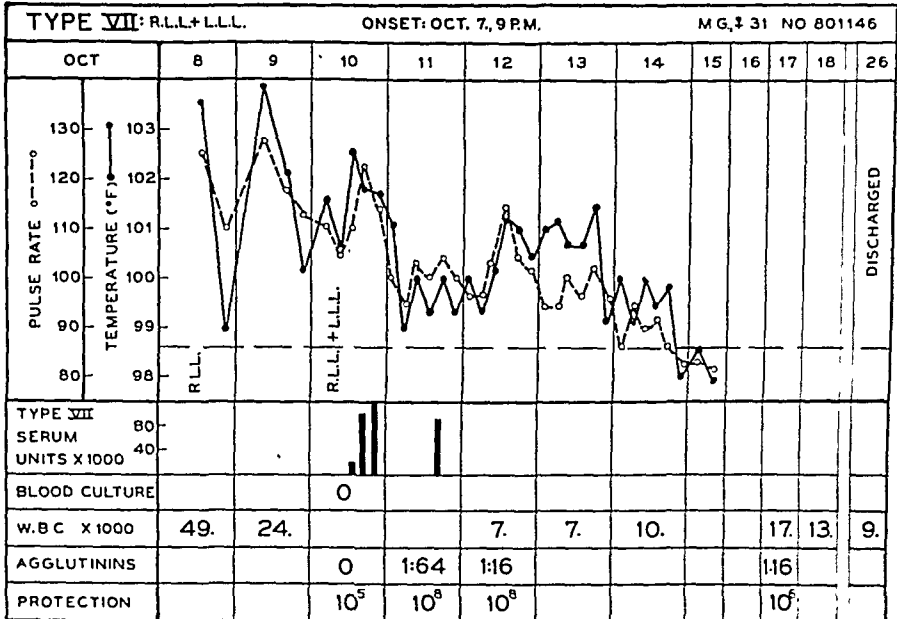
CASE 10.

Cases in Which Crisis Occurred More Than 24 Hours After Serum Treatment. In 3 of these cases, infection with organisms other than

the Type VII pneumococcus may have been responsible for the continued fever and symptoms. Type IX and Type IV pneumococci



CASE 11.



CASE 12.

were isolated from the sputum in Cases 22 and 23, respectively, in addition to the Type VII pneumococcus. *Hemophilus influenza* was also cultured in these 2 cases. The Type VII pneumococcus

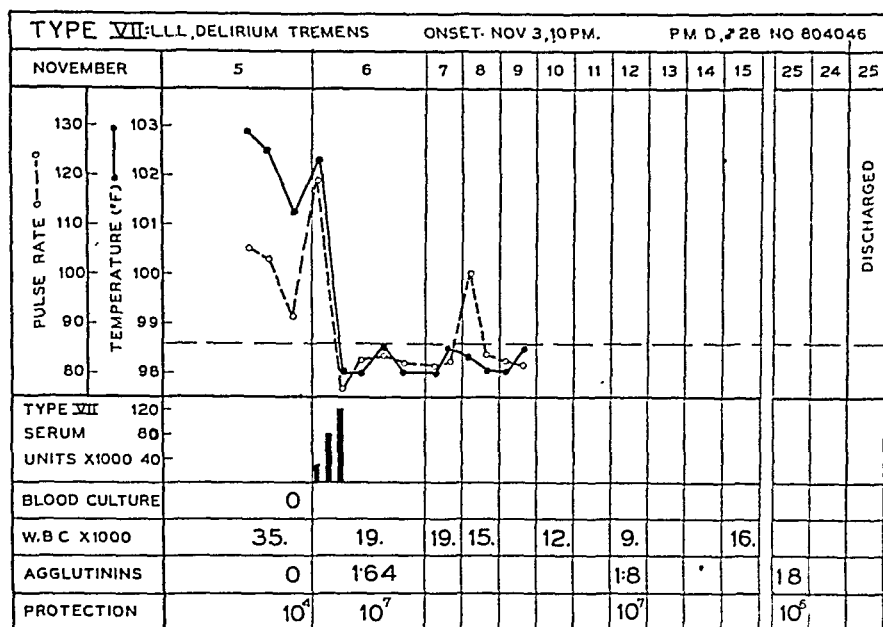
pneumonia occurred in the course of active pulmonary tuberculosis in Case 28, and tubercle bacilli were identified in the sputum from this case after the symptoms of pneumonia subsided. In Case 6, a recurrence of fever after serum therapy was followed by the appearance of signs of bronchopneumonia in the lung opposite to the site of the original and typical lobar pneumonia. A second sputum "typed" in the usual manner showed that the Type VII pneumococci were still present but adequate search for other organisms was not made.² ⁸ Case 10 was that of a woman whose pneumonia began on the day before admission and who, soon after entry, was delivered of a living premature baby. Treatment on the next day with 240,000 units of antibody was followed by an apparent crisis with sterilization of the blood stream within 12 hours. There was a recurrence of fever for 2 days, without symptoms referable to pneumonia. This fever was considered to be incident to the puerperium. In Case 12, the lesion had extended contralaterally at the time that serum was first administered. The patient was much improved following treatment, but low-grade fever persisted for 3 days. In Cases 18 and 26, the blood culture taken before the institution of serum therapy was positive for *Pneumococcus* Type VII, the former showing 57 colonies per cc. of blood in agar pour plates. A dose of 100,000 units in the former and 80,000 units in the latter was followed by marked improvement but was apparently not quite adequate. Further improvement followed the injection of additional amounts of antibody, 120,000 units in the former and 60,000 units in the latter case. In Case 3, the symptoms were only slightly improved by serum therapy. In this case, Type VII pneumococci were obtained from 2 samples of sputum examined in the routine manner.

Effect of Serum Treatment Begun After the Fourth Day. Two of the 4 patients to whom serum was first exhibited early in the fifth day had a delayed response associated with mixed infections and have been mentioned above (Cases 22 and 28). The other 2 were free of symptoms on the day after serum treatment, except for a slight rise in temperature for 3 to 6 hours (Cases 5 and 9). Of the 3 patients treated on the sixth day or later, 2 died (Cases 8 and 29) and the third (Case 26) had bacteremia and a delayed recovery.

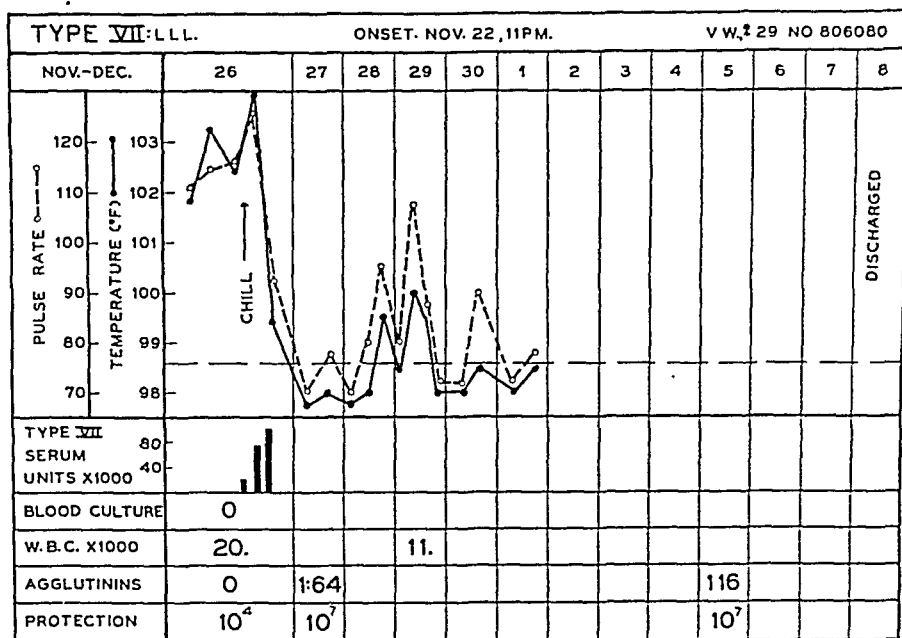
Bacteremic Cases. Blood cultures made before the first injection of serum were positive in 5 patients, 1 of whom died (Case 8). In the 4 patients who recovered, the blood was rapidly sterilized following serum therapy. In 3 cases, however, complete relief of the acute symptoms of pneumonia was delayed until after additional amounts of antibody had been given.

Complications. No purulent complications of the pneumonia were encountered. One patient, Case 16, developed a sterile pleural effusion during the second week of convalescence, and another patient, Case 4, had an acute tonsillitis with hemolytic streptococci in the pharyngeal cultures during the third week.

Serum reactions were relatively uncommon. Only 2 patients experienced *chills* after any of the injections: 1, Case 14, after the



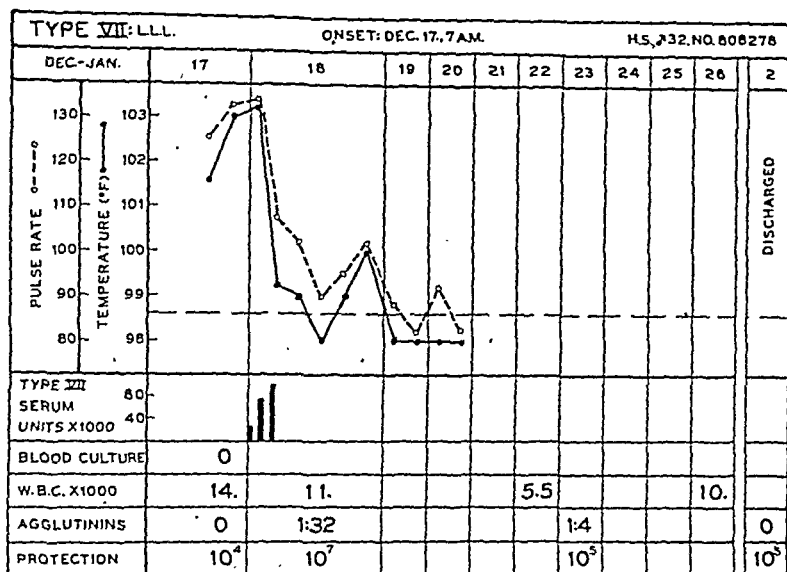
CASE 13.



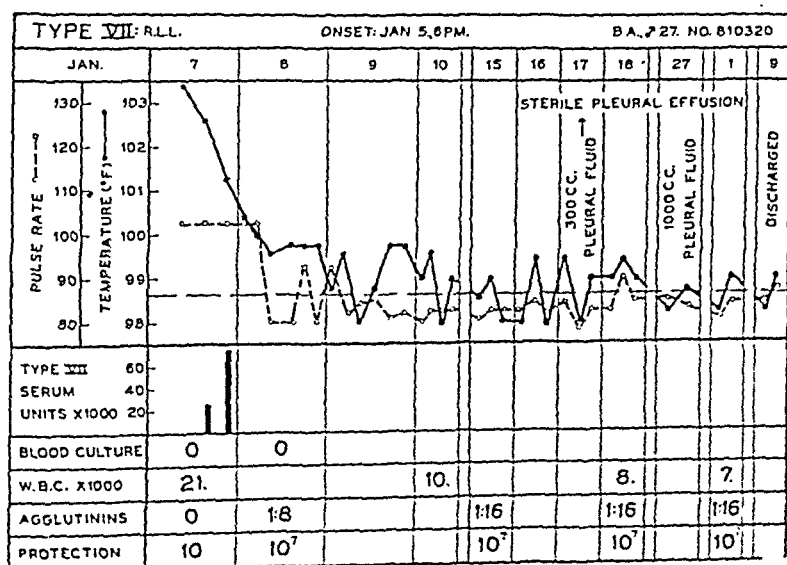
CASE 14.

initial injection of 30,000 units contained in 5 cc. and the other, Case 2, after the third injection consisting of 100,000 units contained in 20 cc. of the concentrated antibody. One patient, Case 23, who

had received therapeutic diphtheria antitoxin 15 years previously, had mild urticaria following the first injection and was promptly



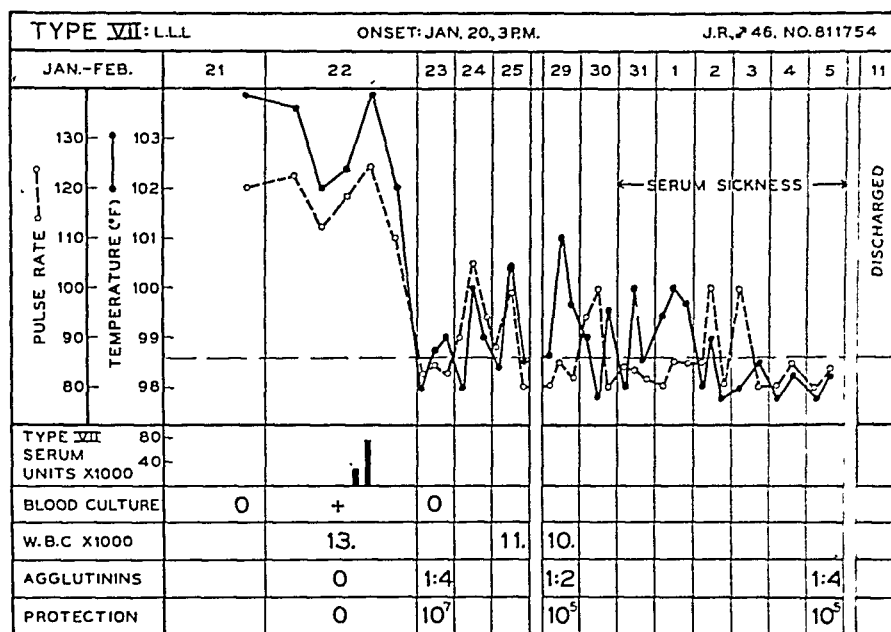
CASE 15.



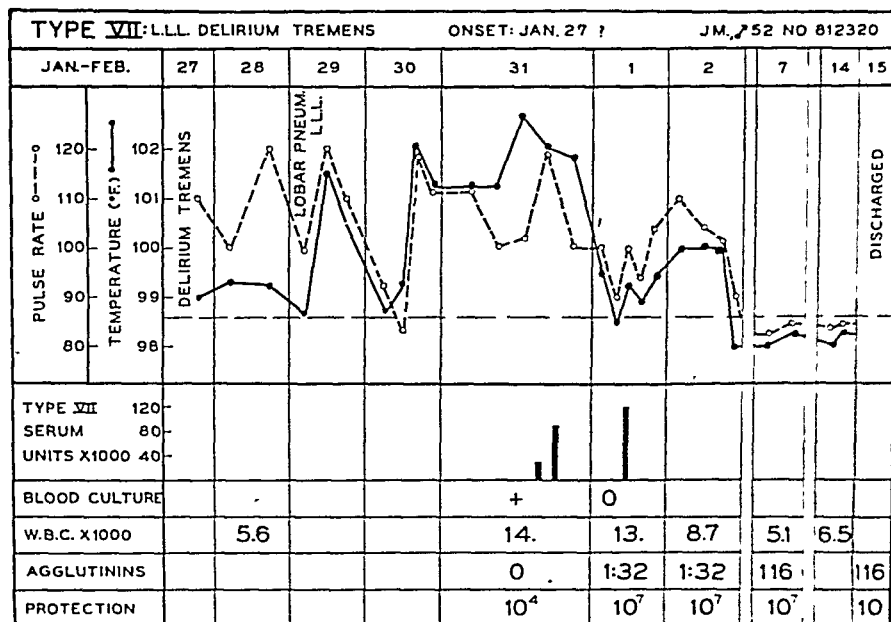
CASE 16.

relieved by a small subcutaneous injection of adrenalin. Another patient, who had long suffered from chronic bronchitis, experienced slight substernal oppression and wheezing after the second injection

and was also promptly relieved by an injection of adrenalin. *Serum sickness* occurred in 7 patients (see charts) and was mild in every instance.



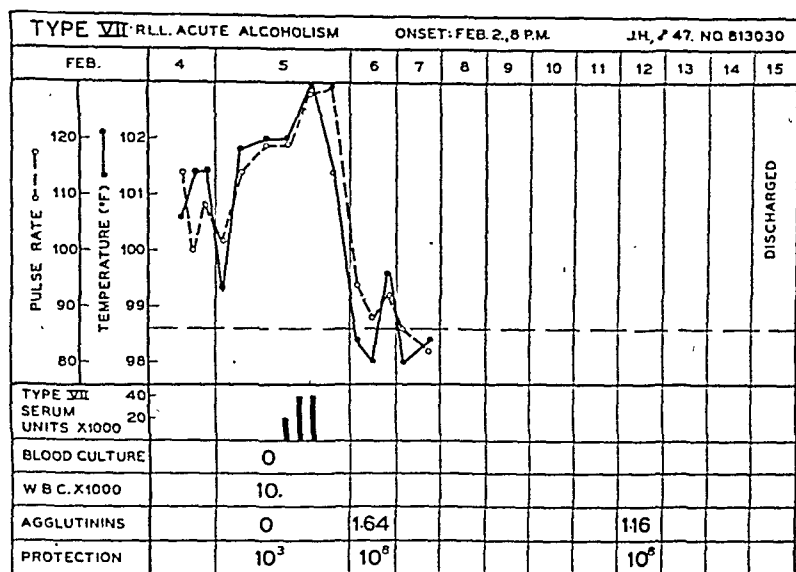
CASE 17.



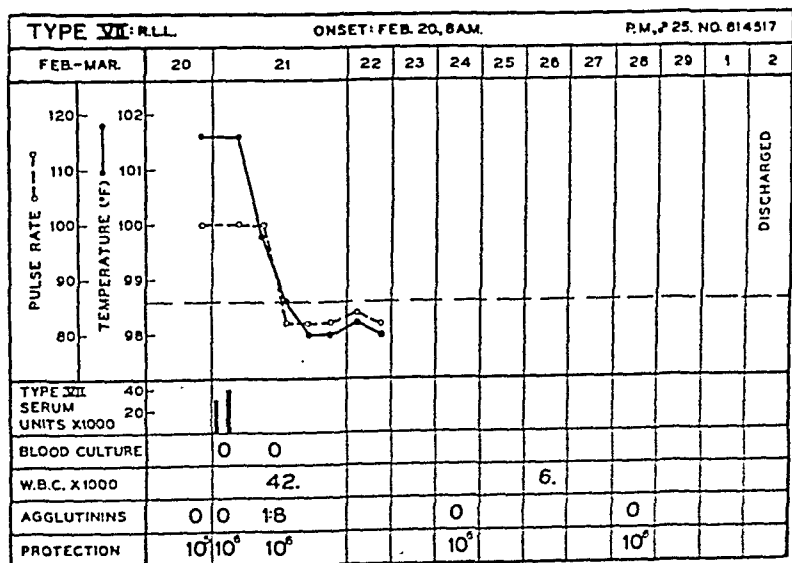
CASE 18.

In brief, therefore, it may be said that with the exception of 1, or possibly 2 cases, the failure to demonstrate a clinical crisis in

direct response to treatment with specific serum could be accounted for by the same factors which interfere with the complete thera-



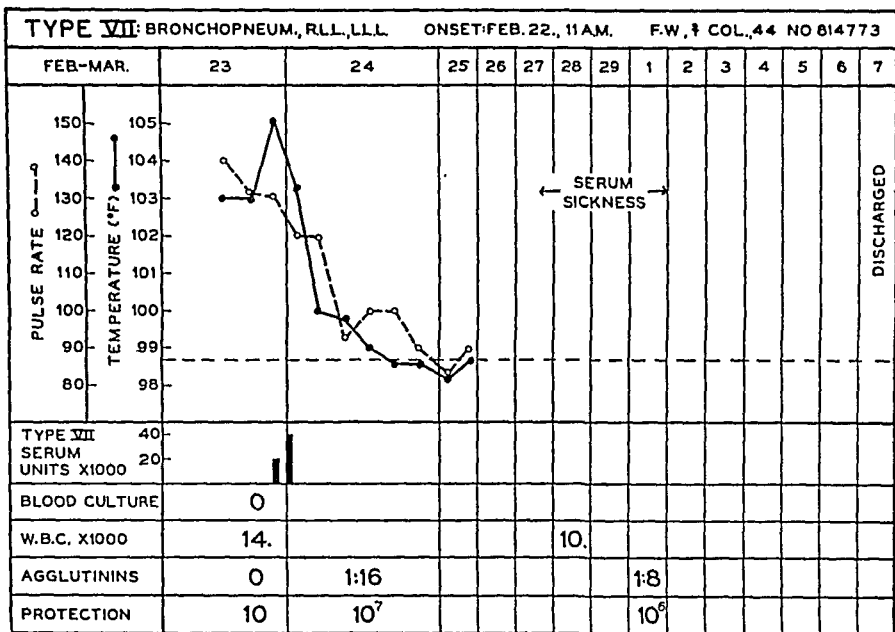
CASE 19.



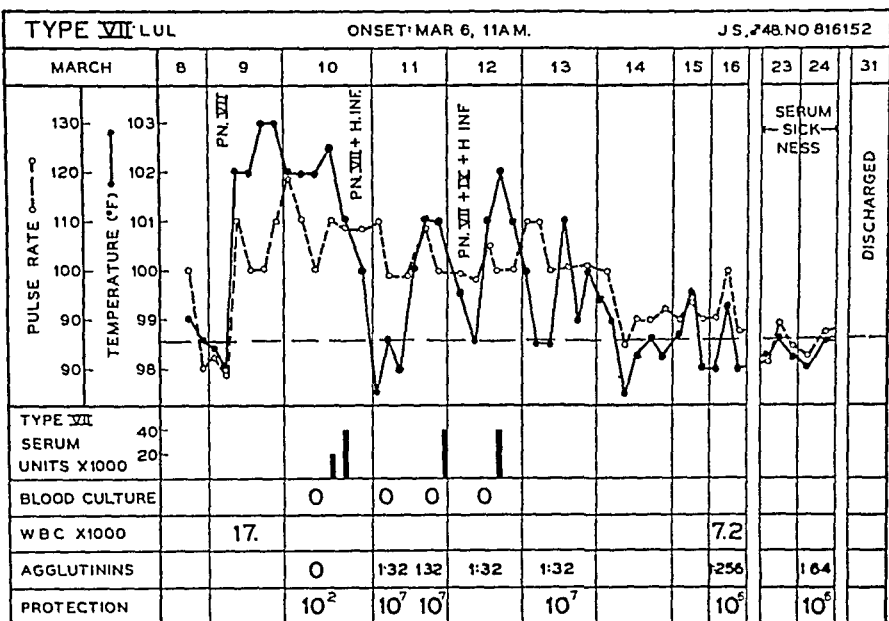
CASE 20.

peutic efficacy of specific antibody in cases of Pneumococcus Type I pneumonia.^{2b} These factors include chiefly: 1, "mixed infections," 2, delayed treatment, 3, inadequate dosage, particularly in the

presence of bacteremia and extensive lesions, and 4, the presence of complications. Treatment on the fifth day, in the absence of the



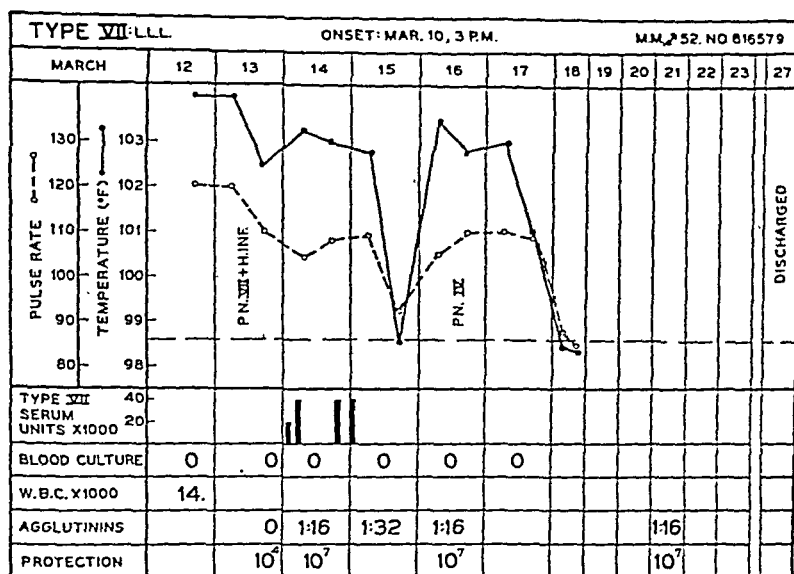
CASE 21.



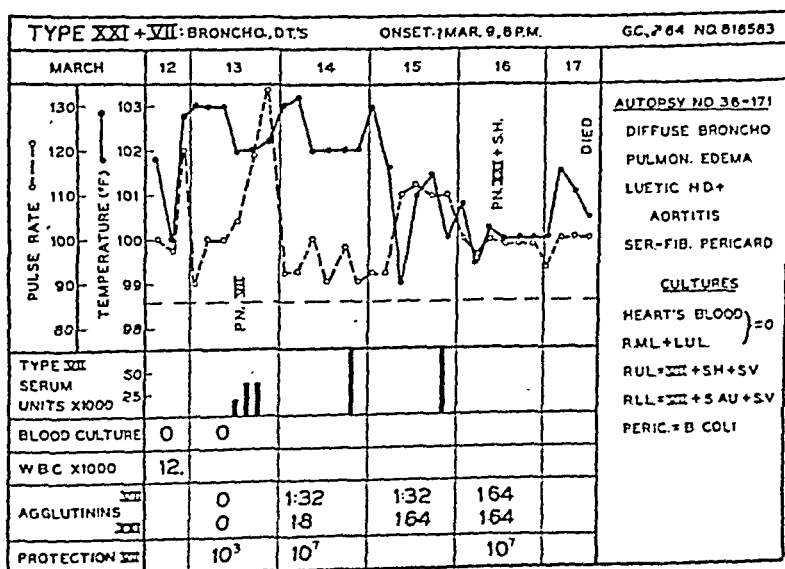
CASE 22.

other factors noted, was apparently efficacious, but when begun on the sixth day or later, it was not successful.

Results of Serological Tests. Tests for Type VII pneumococcus agglutinins were made on the sera of all patients before the first



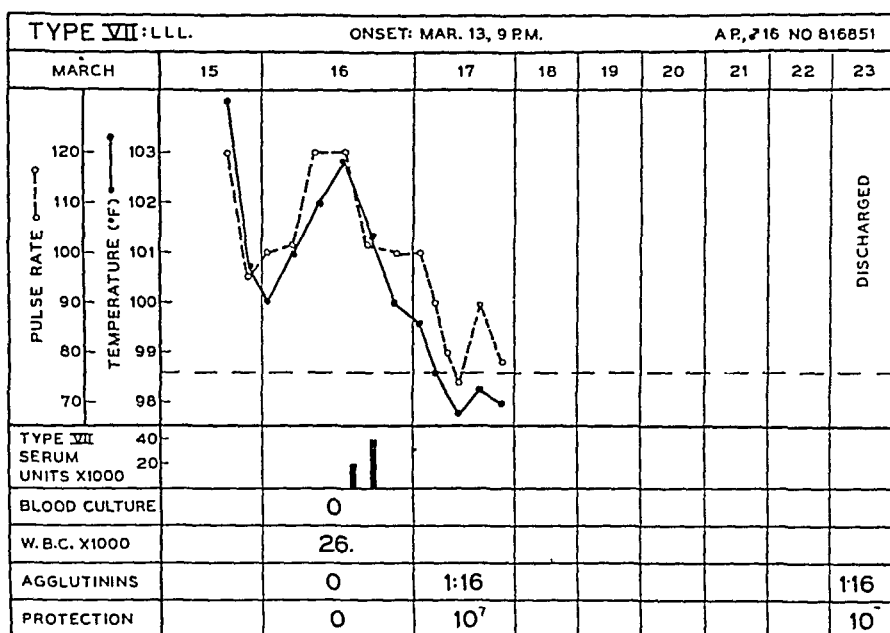
CASE 23.



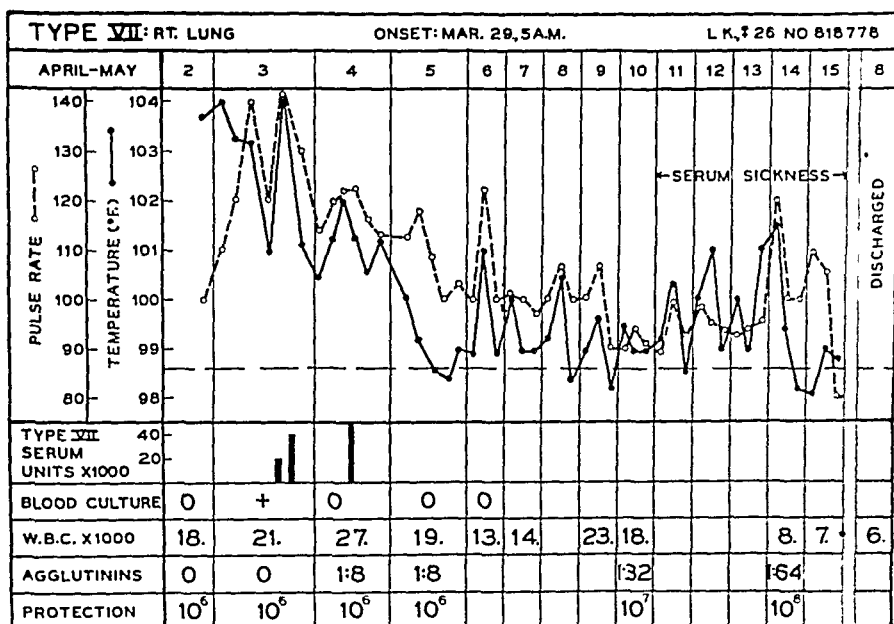
CASE 21.

dose of therapeutic serum was given and, except in Case 8, further tests were made after treatment. Tests for the homologous type mouse protective antibody were also carried out on the sera ob-

tained before and after specific therapy in all but 6 of the cases. The results of all these tests are shown in the charts.



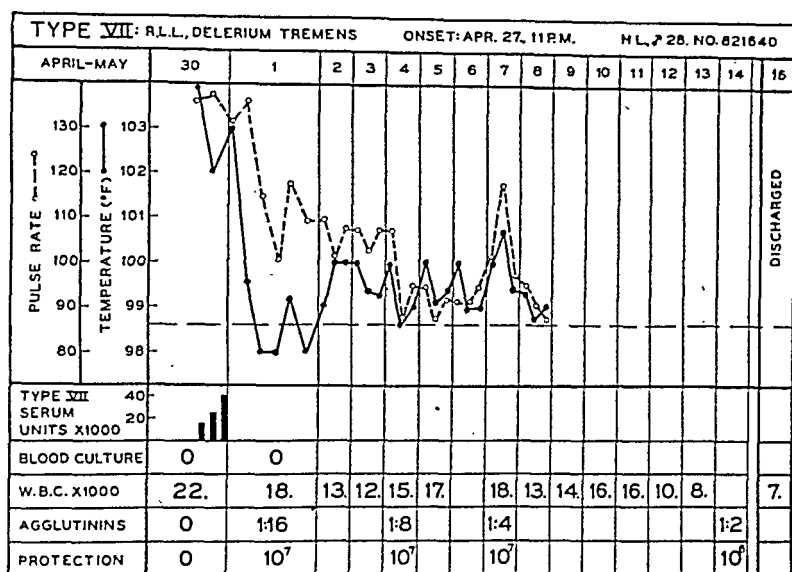
CASE 25.



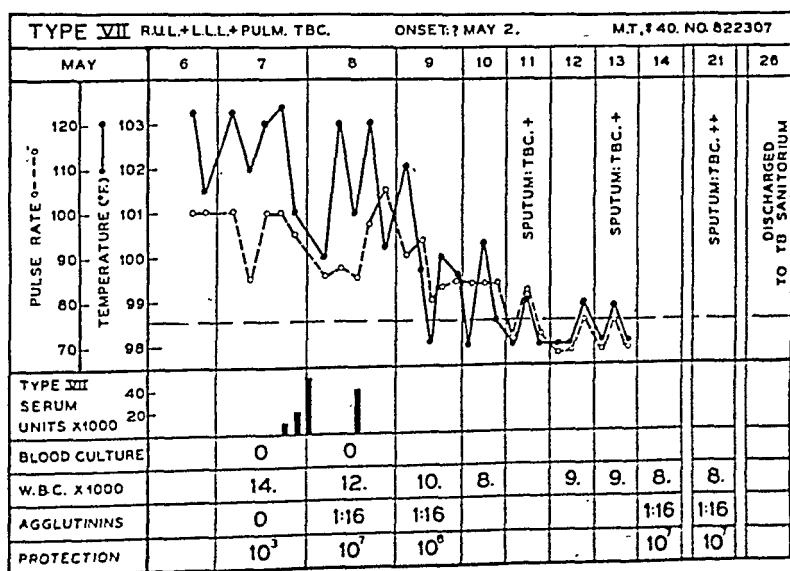
CASE 26.

Agglutinins for Type VII pneumococci could not be demonstrated in any of the bloods taken before specific treatment, except in Case 29. Two different specimens from this patient, one taken at

the time of admission and another taken before the first injection of therapeutic serum a few hours later, each showed floccular agglu-



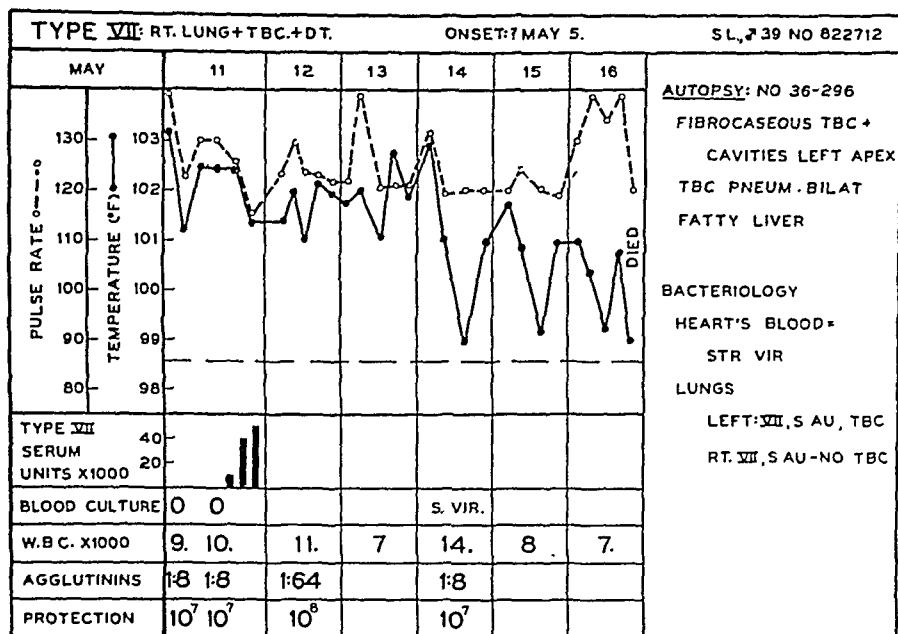
CASE 27.



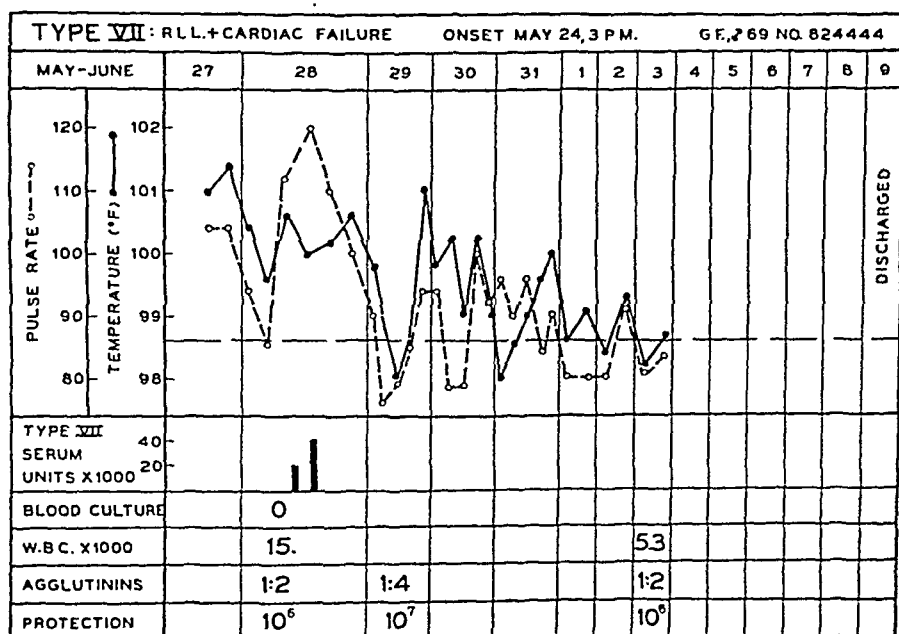
CASE 28.

tionation in 1 to 8 dilution of the serum. Every specimen of blood taken after specific therapy showed Type VII agglutinins in 1 to 4 or greater dilution of serum.

In each of the 3 patients who had another pneumococcus type in the sputum in addition to the Type VII tests for agglutinins were



CASE 29.



CASE 30.

carried out with both types. Agglutinins were not demonstrated in the earlier specimens of serum from any of these patients. In Case 22, agglutinins for Type IX pneumococcus in 1 to 2 and 1 to 4

dilution were demonstrated in the later sera; in Case 23, agglutinins for Type IV could not be demonstrated in any of the sera tested and in Case 24, a high titer of agglutinins for Type XXI developed and was maintained. To what extent the antibodies contained in the therapeutic serum contributed to the positive results with the Types IX and XXI pneumococci is not certain. However, tests with the same antigens made on the sera of several other patients after treatment with the same or similar therapeutic antisera gave essentially negative results.

Mouse protective antibodies for Type VII pneumococcus were present in the patients' serum *before* treatment in all but 6 of the 24 cases in which tests were made. In 10 of these cases, the titers were comparable to those of the homologous type antibody attained during convalescence from pneumonia due to Types I, II, III, V, and VIII^{4,6a,b} in patients treated without specific serum (protection against 50,000 or more fatal doses per cc. of serum). In the remaining 8 patients, lower titers were encountered (50 to 5000 fatal doses per cc. of serum) before treatment. The sera obtained after specific therapy all showed uniformly high titers of protection for the homologous type pneumococcus which were usually maintained at about the same level. In some cases, the titers were higher than those observed with any other type of pneumococcus of similar virulence for mice, several of the sera, in 0.2 cc. amounts, protecting mice against 0.1 cc. of culture, or the equivalent of 100,000,000 fatal doses. Protection tests for types other than Type VII were not done.

In view of the fact that it is unusual to demonstrate homologous type-specific antibodies by agglutination or by passive protection in mice during the first few days of illness in non-serum treated cases of pneumococcus pneumonia of other types,^{4,6a,b} most of the positive tests in sera obtained before therapy were repeated—with identical results. Control tests for the virulence of the cultures were always performed at the end of each protection experiment during which from 3 to 15 sera were tested and which always required less than 30 minutes from the time the culture dilutions were made. One or both of 2 control mice injected with 0.000,000,001 cc. of culture almost invariably died within 72 hours. This amount of culture was considered to contain 1 lethal dose. Mice injected with greater amounts of culture invariably succumbed within the same interval. Blood agar plates containing 0.000,000,1 cc. of culture yielded 70 to 130 colonies in various tests.

Control tests in patients with pneumococcus Type VII pneumonia treated without serum and in non-pneumonic hospital patients have been previously reported.¹¹ Although the number of observations made early in the course of the disease were few, the occurrence of homologous mouse-protective antibody and, occasionally, also agglutinins, before the time of crisis was noted. These antibodies were also demonstrated in some fatal cases and, in certain instances, in the same blood from which the homologous type pneumococcus

was cultured. Of 26 non-pneumonic subjects, 19 were shown to have Type VII protective antibody for 100 or more fatal doses in 0.2 cc. of serum. In 6 of these, the serum protected against 100,000 fatal doses. Additional observations in 9 cases of pneumonia and in 6 non-pneumonic subjects are shown in Table 1. All of the previous findings are here corroborated.

TABLE 1.—PNEUMOCOCCUS TYPE VII ANTIBODIES IN NON-SERUM TREATED CASES OF PNEUMONIA DUE TO THIS TYPE AND IN NORMAL ADULTS. (SEE ALSO (1)).

Case.	Age (yrs.)	Termination.		Sputum.	Blood culture.		Serological.		
		Mode.	Day.		Day	Result.	Day.	Agglutinins. (serum dilution).	Protection. (Fatal doses per 0.2 cc. serum.)
J. M.	37	Lysis	7-9	VII	9	0	9	1:8	
J. L.	37	Lysis	9-11	VII	8	0	8	1:2	10 ³
F. S.	47	Lysis	8-10	VII	8	VII	8	0	10 ⁶
J. R.	25	Lysis	7-10	VII	6	0	16	1:32	
D. McD.	50	Crisis	9	VII	2	0	2	0	
					6	0	6	0	
					7	VII	14	1:8	
					8	0	20	1:16	
					8	0	10	0	
C. C.*	23	Crisis	9	VII	8	0	10	0	
J. D. G.	52	Died	9	VII	4	VII	5	0	10 ²
					5	VII	7	1:16	10 ⁵ +
					7	0			
J. McG	52	Died	14	VII	A	0			
					14	VII	14	0	10 ⁴
H. W.	72	Crisis	2	VII	A	VII			
					2	0	2	1:2	10 ⁶
							11	1:64	10 ⁷
S. K.	50			Normal Subject				0	10 ⁴
J. B.	40			Normal Subject				0	10 ⁴
C. M.	37			Normal Subject				0	10 ⁵
D. K.	40			Normal Subject				0	0
G. W.	50			Normal Subject				0	10 ⁴
C. M.	25			Normal Subject				0	10 ⁴

* Upper respiratory infection without pneumonia, Type XXIV in sputum also. No agglutinins for Type XXIV in serum on 10th day. A=autopsy.

Discussion. No final conclusions can be drawn with regard to the efficacy of a therapeutic agent in pneumonia without adequate consideration of all of the factors entering into the outcome in this disease. The proper evaluation of specific therapy for pneumonia due to the less common types of pneumococci would necessarily require observations over many years in a large number of suitable clinics. The clinical response to specific therapy in consecutive cases, when considered in the light of the data accumulated in similar groups of cases treated without the specific agent, offers a satis-

factory basis for tentative conclusions. The clinical results noted in the present series of cases, small though it be, strongly suggest that concentrated specific antibody, as here employed, has a favorable effect on the course of *Pneumococcus* Type VII pneumonia. Together with the results already reported by Bullock,^{1,2,3} they suggest further that its use in adequate amounts early in the disease results in a reduction in death rate among cases of pneumonia due to this type.

The results of the immunological tests are of interest chiefly because they differ from the findings in cases of pneumonia due to the more common types of pneumococci, in which protective properties do not appear until about the time of recovery. When considered together with the finding of pneumococcal properties for the homologous type early in the disease in the blood of patients with Type I pneumonia,^{9,10} they offer further basis for speculation with regard to the interrelationship of various immunological reactions and the significance of each, in turn, for resistance to or recovery from pneumococcus infections. It may be significant that, with the Type VII pneumococcus, as with most of the other specific types investigated, antibodies demonstrable by the agglutination test are not found in normal individuals nor in the first few days of pneumonia due to this type. A balance of the antibody is readily established, however, by the administration of adequate amounts of the specific antibody.

With regard to dosage, the experience in the later cases of this series in which, owing to the limited supply, smaller amounts were used, would indicate that doses of 80,000 to 100,000 are adequate for most uncomplicated cases if the blood is sterile before treatment. Twice that amount is probably required in cases with bacteremia and, possibly, also in those whose pulmonary lesion has extended before treatment. More experience is necessary with cases of varying severity and in various types of patients before the dose can be more adequately defined.

Summary and Conclusions. In a series of 30 cases of *Pneumococcus* Type VII pneumonia, rapid and permanent clinical improvement followed treatment with concentrated type-specific antibody with great regularity, except under certain well-defined conditions.

Immunological studies in these cases showed that a sufficient balance of homologous antibodies (agglutinins and mouse protection) can be established and maintained in the blood of patients with Type VII pneumonia by adequate treatment with concentrated type-specific antibody solutions.

Mouse protective antibody for the homologous type of pneumococcus was demonstrated in relatively high titers during the acute disease and before serum treatment in a large proportion of cases of Type VII pneumonia. This antibody was also found in the serum

of most of the normal adults thus far tested. Type-specific agglutinins were not demonstrated under these conditions.

The immunological studies were carried out with the technical assistance of Mildred W. Barnes.

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AGENESIS OF THE LUNG.

A REVIEW OF THE LITERATURE AND REPORT OF A CASE.*

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FAILURE of development of a lung is an exceedingly rare occurrence. Only 34 authentic cases of agenesis of the lung are adequately recorded in the literature (Table 1). A description of the following case then seems warranted.

Case Report. C. H., a white female infant, aged 7 weeks, was admitted to the University of California Hospital because of stertorous breathing since birth. There was no cyanosis or dyspnea but the respirations were "noisy." Roentgenograms taken by the family physician were interpreted as showing "massive atelectasis of the left lung." Carbogen inhalations, however, did not alter the condition. Examination showed a well nourished infant breathing noisily, particularly on inspiration, but without respiratory distress. The left side of the chest did not move so freely as the right. The heart was displaced to the left and the apical impulse was very forceful. There was definite flatness over the whole left side of the thorax. Suppressed bronchial breath sounds were audible over this area. Otherwise, except for a partially bifid uvula, there were no unusual physical findings. Wassermann and tuberculin tests were negative. The blood count showed a hemoglobin of 85% (Sahli); 3,400,000 red blood cells and 12,650 white

* Supported by the J. J. and Nettie Mack Foundation.

TABLE 1.—RECORDED CASES OF CONGENITAL ABSENCE OF THE LUNG.

Author.	Case.	Absent lung.	Findings.
1. Haberlein (Akad. zu Wien., 1, 271, 1787)	Soldier, 20 years	Left	No left pulmonary vessels or bronchus. Left thorax filled with watery fluid. Right lung normal.
2. Hein (Wehnschr. f. d. ges. Heilk., p. 536 1837)	Male, 6 weeks—cyanosis	Right	Right pulmonary vessels absent. Rudimentary right bronchus. Defect in the ventricular septum. Patent foramen ovale. Pulmonary artery closed at the base of the heart; left lung supplied by the ductus arteriosus.
3. Maschka (Allg. Wien. med. Ztg., p. 78, 1862)	Child, miscarried at 7 months; lived 2 hours	Right	Heart in right side of thorax. Bronchus represented by pea-sized sac. Right pulmonary vessels absent. Left lung not lobed. Esophagus ended blind at midpoint. Atresia ani.
4. Grüber, W. (Oesterr. Ztschr. f. prak. Heilk., 16, 7, 1870)	Female, still-born	Right	No right pulmonary vessels or bronchus. Left lung unilobar with only one pulmonary vein.
5. Herrero, F. (Corresp. Med., 9, 372, 1874)	Male, 65 years	Left	Undivided trachea continuous with right bronchus. Right lung enlarged.
6. Stein (Fürst. Gerhard's Handb. d. Kinderkr., 3, 553, 1878)	Infant, 6 weeks	Right	Pulmonary vessels completely absent. Rudimentary right bronchus.
7. Haberlein (Rev. mens. d. mal. de l'enfance, 2, 554, 1884)	Soldier, 24 years	Right	No right bronchus. Pulmonary artery entered undivided into the left lung. Right hydrothorax. Left lung enlarged with two bronchi entering it.
8. Theremin (Rev. mens. d. mal. de l'enfance, 2, 554, 1884)	Female, 11 days	Left	Trachea continuous with right bronchus. Small cartilaginous nodule at the site of the left bronchus. Right lung unilobar. No pulmonary veins entered left auricle; united to form a large vessel that communicated with a distended vena azygos.
9. Theremin (Rev. mens. d. mal. de l'enfance, 2, 554, 1884)	Female, 127 days	Left	Trachea continuous with the right bronchus. Left pulmonary vessels
10. Grüber (Virchow's Arch., 102, 11, 1885)	Female fetus	Left	lung not lobed. The pulmonary artery divided into a right branch and the ductus arteriosus. One vein emptied into the left auricle.
11. Bell (Anat. and Physiol. of Human Body, 5th ed., p. 416)	Young male	Left	Left hydrothorax.
12. Bell (Ibid.)	Male, 24 years. Respiratory difficulty since birth	Right	Both bronchi entered the left lung. No right pulmonary vessels.
13. Müller (Trudi Obshtsh. dietsk. Vrach., 3, 32, 1891-95)	Male, 4 weeks	Pea-sized left lung attached to a thin bronchus. Pneumonia of right lung.
14. Müller (Ibid.)	Male, 6 weeks	Left lung cherry size attached to a narrow bronchus.
15. Müller (Ibid.)	Female, 2 days	Left lung 2 cm. in diameter attached to a narrow bronchus.
16. Tichomirow (Internat. Monatschr. f. Anat. u. Phys., 12, 24, 1895)	Female, 21 years; died of pneumonia	Left	No left bronchus. Trachea divided into three bronchi before entering the right lung.
17. Hanson, R. (J. Am. Med. Assn., 37, 701, 1901)	Female, full term; lived 15 minutes	Left	Bronchus 1/4 inch long. Heart on the right side. Right lung smaller than normal. Diaphragm lacking on the left side with lower portion of the small intestine and part of the colon in the left pleural cavity.
18. Findlayson (Proc. Anat. Soc. Great Britain and Ireland, vol. 38, 1901-02)	Infant. Lived a few hours after birth	Right	Trachea ended in the left bronchus. Pulmonary vessels undeveloped. Left lung hypertrophied.

TABLE 1.—RECORDED CASES OF CONGENITAL ABSENCE OF THE LUNG.—(Continued.)

Author.	Case.	Absent lung.	Findings.
19. Gross, W. (Ziegler's Beitr. z. path. Anat., 37, 487, 1905)	Male, 5 months, 23 days.	Left	Blind left bronchus. Left pulmonary vessels absent. Right lung enlarged; no lobulation. Other lesions included left-sided hypoplasia of face, dermoid of left eye, anomalous right renal artery and atresia ani.
20. Ellis, A. G. (AM. J. MED. SCI., 154, 33, 1917)	Male, 8 years	Left	Absent pulmonary vessels. Right lung enlarged with five lobes. Hydro-pericardium and vegetations on the mitral valve.
21. Tebbutt, A. H. (Med. J. Australia, 2, 430, 1918)	Male, 12 years	Left	Heart in left thorax. Pulmonary artery divided into two branches before entering the right lung. Pericardial adhesions. Endocarditis of the mitral and aortic valves.
22. Jarisch (Wien. klin. Wchnschr., 32, 736, 1919)	Soldier, 29 years. Dyspnea and cyanosis. Left side of chest flattened. Needled as an empyema; blood obtained	Left	No pleura. Left bronchus present as a short stump. Mediastinum displaced to the left with the heart against the left chest wall. Slight hemorrhagic pericardial fluid. Enlarged, imperfectly fissured right lung showing bronchopneumonia.
23. Levy, C. S. (AM. J. MED. SCI., 159, 237, 1920)	Male, 49 years. Thorax asymmetrical	Left	No left bronchus or pulmonary vessels. Right lung enlarged; lobular pneumonia. Also had lues.
24. Muhamed, K. S. N. (Indian Med. Gaz., 58, 262, 1923)	Female, 19 years. Death from fall into a well	Left	Thickened upper left pleura. Trachea undivided entered the right lung. Right lung enlarged. Heart displaced to the left; pericardium full of blood. Two thymus glands, one in the left pleural cavity. Ruptured spleen and liver with the peritoneal cavity full of blood.
25. Dannheiser, F. (Beitr. z. path. Anat., 76, 87, 1926)	Male, 34 years. Died of a skull fracture	Left	Left, above and behind the arch of the aorta, was some hemorrhagic adipose tissue. The enlarged right lung reached into the left pleural cavity and was not fissured. No septum membranaceum along whole trachea. The latter had 26 cartilage rings and divided into two branches, both entering the right lung. Heart displaced to the left; ductus Botalli obliterated. Meckel's diverticulum and anomalous kidney vessels.
26. Heerup, L. (Hospital, 70, 1165, 1927)	Female, 72 years. Died of cerebral hemorrhage. Emphysematous chest. Left side dull, bronchial breathing, occasional sonorous râles, accentuated heart sounds on this side. Visible cardiac pulsations to the left of the sternal border. Diagnosed as left pleuropneumonia.	Left	Left half of thorax filled by the large heart, pericardium, great vessels and some adipose tissue. The right lung was hypertrophic and emphysematous, and extended over to the left midclavicular line covering the medial portion of the heart. The latter was displaced to the left.
27. Gilkey, H. M. (J. Mississippi Med. Assn., 25, 296, 1928)	Male, 6 months. Diagnosed before death. Respiratory distress and absent breath sounds on the right side.	Right	Congenital absence of right radius. Mediastinum and trachea displaced to the right.
28. Welsch, K. (Frankf. Ztschr. f. Path., 36, 192, 1928)	Male, 58 years. Died after motor accident	Right	Absent pulmonary vessels and vagus nerve. Heart and mediastinum displaced to the right. Slight cardiac hypertrophy. Hypertrophy of left lung; hypostatic pneumonia. Increased tracheal cartilage rings. At the left hilum two branches of the trachea were given off to the upper lobe and one to the lower. Slight scoliosis in thoracic region.

TABLE 1.—RECORDED CASES OF CONGENITAL ABSENCE OF THE LUNG.—(Continued.)

Author.	Case.	Absent lung.	Findings.
29. Finner (Clifton Med. Bull., 18, 35, 1932)	Male, 22 months. Dyspneic, cyanotic and clammy	Right	Complete absence of pulmonary artery and bronchus. Peanut in trachea. Mediastinum displaced to the right. The heart in the right hemithorax. Emphysematous left lung. Heart filled the left chest. Slight pericardial fluid. Right lung enlarged with no fissures. Exencephaly.
30. Minne and Gernez (Ann. d'anat. path., 10, 503, 1933)	Female, newborn. Born dead	Left	Suprarenals atrophic. High left No left pulmonary vessels. Enlarged incompletely fissured right lung. Heart filled left thorax. Accessory spleen.
31. Hepner (Arch. f. Kinderh., 103, 92, 1934)	Female, 3 months. Cyanosis and sternal retraction; terminal fever; chest tap yielded blood. Diagnosed as congenital bronchiectasis	Left	
32. Knott (Ztschr. f. Kinderh., 56, 338, 1934)	Male, 5 weeks	Right	Right bronchus absent. Dextrocardia and mediastinum displaced to the right. Hypertrophied left lung; bronchopneumonia.
33. Dyson, J. E. (J. Iowa Med. Soc., 24, 442, 1934)	Female, 6 months; 8 months premature. Left side of chest flattened. Diminished respiratory movement, flatness, and absent breath sounds	Left	No left pulmonary vessels or bronchus. Right lung showed edema, emphysema and interstitial pneumonia.
34. Toni, C. (La clin. ped., 16, 241, 1934)	Female, 4 months. breath sounds heard on both sides. Lipiodol injection unsuccessful because of cyanosis. Clinical diagnosis: diaphragmatic hernia	Right	Heart and mediastinum displaced to the right side. Hypertrophied left lung; bronchopneumonia.

blood cells with 37% neutrophils. The roentgenologist reported a complete collapse of the left lung with a shift of the heart and mediastinal structures into the left side of the thorax. Fluoroscopy, after a small amount of barium by mouth, showed the esophagus to be about 2 cm. to the left of the midline and slightly angulated (Fig. 1). There was no evidence of diaphragmatic hernia. Culture of the fasting gastric contents revealed a predominance of *Strep. alpha*.

In view of the difficulty in establishing a definite clinical diagnosis from the physical and Roentgen findings alone, bronchoscopy was decided upon. A tube of 4 mm. in diameter could be passed only a very short distance beyond the vocal cords, as the trachea was definitely narrowed. This procedure was borne well, so that 5 days later another attempt was made to visualize the bronchial tree. Again the stenosis of the trachea prevented the passage of the tube beyond 1 cm. below the vocal cords. Following the second bronchoscopy the temperature became elevated, the respiratory rate increased, and râles were heard at the base of the right lung. There was increasing dyspnea, and death occurred 2 days later.

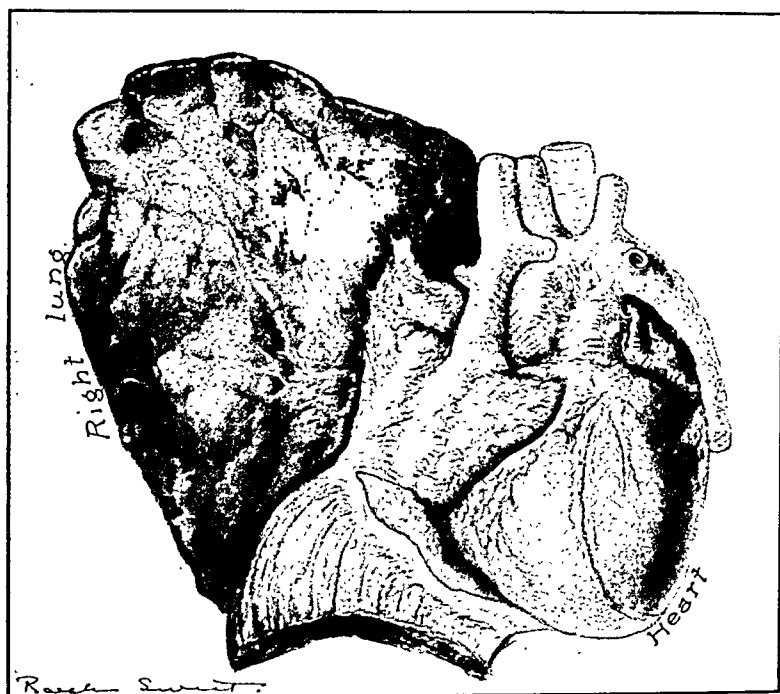
NECROPSY (3 hours after death) showed the left pleural cavity to be entirely obliterated because of the almost complete absence of the left lung and the adherence of the parietal pleura and pericardium. The right pleural cavity contained neither free fluid nor adhesions. The mediastinum was displaced to the left and occupied the entire left side of the thorax. The thymus was present in the anterior mediastinum, and was normal in size. The middle mediastinum extended to the midaxillary line and con-



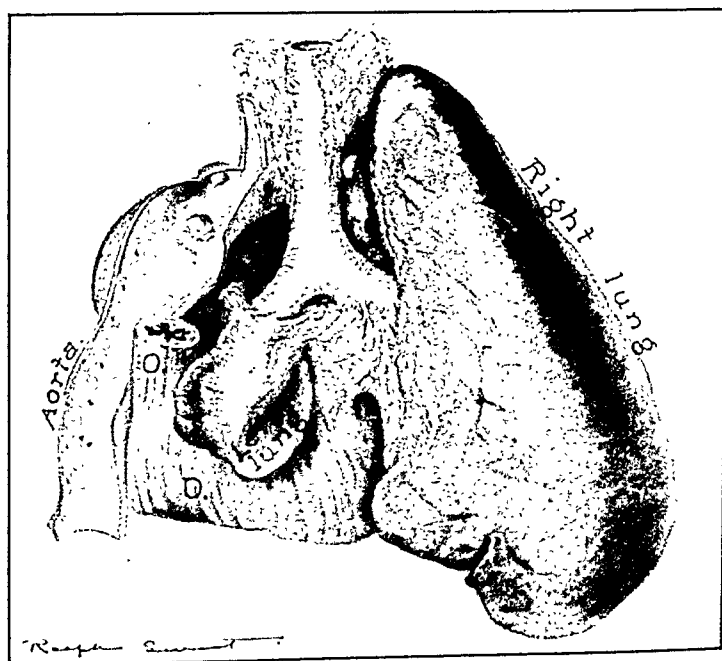
FIG. 1.—Roentgenogram showing absence of the normal lung shadow on the left side. Note the displacement of the esophagus. The left cardiac border is not visible.



FIG. 3.—High-power magnification of the rudimentary left lung (Mallory's connective-tissue stain); A, broad band of connective tissue; B, atelectatic alveoli.



A



B

FIG. 2.—Drawings of the thoracic contents showing the structural relationships observed at postmortem: A, anterior view; B, posterior view. Note the hypertrophied monolobar right lung.

tained a slightly dilated heart. The ductus arteriosus, foramen ovale and intraventricular septum were all occluded. The three main branches of the aortic arch came off at their normal positions. A single pulmonary artery from the right ventricle passed to the right lung. The venous return from this lung emptied into the left auricle. The rudiment of tissue which represented the left lung weighed $2\frac{1}{2}$ gm. and was attached to the end of a short narrow bronchus. It was of a reddish hue and firm in consistency. Only one vessel was seen entering the rudimentary left lung, and this appeared to be a vein which emptied into the azygos vein on the right side. The right lung, consisting of only one lobe, was hypertrophied and extended just beyond the midline (Fig. 2). Definite narrowing of the trachea was confirmed. No abnormalities were found in the other organs.

Microscopically, the sections of the rudimentary left lung showed broad bands of connective tissue characteristic of the fetal lung (Fig. 3). A few alveoli were noted, the greater portion being atelectatic. The right lung showed evidence of an inflammatory reaction.

Discussion. Although embryologists are not in entire agreement as to the developmental anatomy of the respiratory system, the prevailing theory¹ is as follows: A groove-like evagination arises on the ventral side of the esophagus in the embryo 3 mm. in length. From the enlarged posterior ends of the groove, two small lung buds grow out. Later in development, the fundaments of the trachea and esophagus become separated by a constriction interrupted at the cephalic end of the larynx which is distinguishable at the end of the fifth week. Muscle fibers and cartilaginous rings differentiate from the surrounding mesenchyme at the end of the seventh week. In a later metamorphosis of the lung buds, hollow evaginations grow out into the envelop of connective tissue, enlarge, and continue to branch, producing the tree-like tubular system. On the fine terminal tubules arise small outgrowths which constitute the alveoli.

The etiology of agenesis of the lung is still obscure. The earlier theory of Meckel and Fleischman⁶ explained the condition on a phylogenetic basis, comparing it with that in reptiles. Klebs⁵ thought that the excessive tension of the amnion when the embryo rotated to the left prevented the development of the right lung. This is wholly inadequate, however, to explain absence of the left lung. Eppinger⁵ believed that enlargement and displacement of the thymus was responsible for failure of development of the left lung in Tichomiroff's case. Tichomiroff⁷ believed that hydrops fetalis or some other early intrathoracic disturbance or infection was the cause of this defect. The most rational explanation for aplasia of the lung, however, ascribes the condition to a developmental error of endogenous origin, perhaps primary in the pulmonary vascular system.

The age distribution of the recorded cases shows 3 still-births, 4 patients under 1 week of age, 12 aged 6 months or under, 1 under 5 years, and 14 ranging from 5 to 72 years. Of the 31 cases in which

the sex was mentioned, 18 were males. Absence of the left lung occurred in 22 of the 34 patients.

There are usually no symptoms, though dyspnea and cyanosis have been recorded in a few instances. Stertorous breathing was the outstanding feature in our patient. The general development of these patients is good, and the thorax is symmetrical in the majority of cases, but slight flattening of the affected side (Dyson²), or scoliosis to the affected (Tichomiroff⁷) or unaffected side (Welsch⁵) may occur. Diminished movement on the affected side, as in our case, has been noted. The heart and mediastinal structures are displaced to the side of the absent lung, and the apical impulse may be pronounced. Flatness or dulness over the affected area results, but occasionally some resonance of the lung is heard because of the presence of the hypertrophied remaining lung. Breath sounds may be unaltered under such conditions, but most frequently are absent or suppressed and bronchial in character. Roentgen findings show the displacement of the heart and mediastinal structures, and may also show a slight elevation of the diaphragm and a narrowing of the intercostal spaces on the affected side. The usual interpretation of the roentgenograms is massive atelectasis.

The differential diagnosis is extremely difficult, and only 2 cases have been diagnosed before death (Munchmeyer,⁸ Gilkey³). Massive atelectasis, paralysis of the diaphragm, diaphragmatic hernia, and foreign body in the bronchus must be considered. If the entity of agenesis of the lung is kept in mind, however, it should be possible to suggest such a diagnosis from the physical and Roentgen findings during life. Ruthless needling can only do harm and is to be deprecated. Bronchoscopy, suggested for the first time here, is the rational method for establishing a clinical diagnosis.

There is complete absence of the lung, or in some cases a rudiment of lung tissue which may be at the end of a bronchus, on the side of the trachea, attached to the esophagus, or in the mediastinal tissue. The pleura of the affected side may be completely or partially present. The cavity is filled by either fluid, displaced heart and mediastinal structures, fat bodies or persistent thymus. The bronchus, when present, is usually smaller in diameter and shorter on the affected side. In those cases in which there is no bronchial vestige the trachea may enter the normal lung without bifurcation, or divide into two or three primary bronchi before doing so. Tracheal involvement as evidenced by narrowing of the lumen or an increased number of cartilaginous rings is not uncommon. The pulmonary vessels on the affected side are absent. There may be a single pulmonary artery from the right ventricle to the good lung, and the large aortic vessels may arise from a common trunk. The venous return from the unaffected lung reaches the left auricle by one or two vessels, or may empty into the vena azygos. The remaining lung is usually hypertrophied and the lobulation may

be abnormal. Pneumonia is common, and bronchiectasis has been described. Other associated anomalies recorded are anal stricture, absence of the diaphragm, esophagotracheal fistula, accessory thymus and hypoplasia of the face.

Absence of a lung does not necessarily preclude the person's reaching adult life. In many patients who survive infancy, the agenesis is not the immediate cause of death, and may be but a coincidental finding at necropsy. Heerup⁴ recorded agenesis of the left lung in a female 72 years of age who died of cerebral hemorrhage.

Summary. A case of agenesis of the left lung is described in a 7 weeks' female infant. A review of the literature is given. Bronchoscopy is suggested as an aid in diagnosis; but the use of this procedure is not without danger, as the reported case went on to a fatal termination 2 days following the second bronchoscopy.

Acknowledgement is made to Dr. Francis Smyth for the use of his private case report.

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THE CLINICAL SIGNIFICANCE OF THE EFFECTS OF POSTURE ON BLOOD PRESSURE.

THE POSTURAL TEST AS A MEANS OF CLASSIFYING HYPOTENSION.

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STUDY of the effect of posture on blood pressure is by no means a new subject, for as early as the year 1897 Hill and Barnard¹³ noted the varied responses of the circulatory apparatus of animals to change of posture and in 1905 Crampton⁶ made clinical observations on man relative to the circulatory response to postural change. Within recent years, especially since the year 1925 when Bradbury and Eggleston⁵ described the clinical entity, "postural hypotension," a keener interest has been manifested generally regarding this subject. The effect of posture on blood pressure and pulse rate on normal adults has been reported by Schneider and Truesdell,¹⁹ Mortensen¹⁶ and others.^{11,14,15}

In this study determinations were made as to the effects of posture on the blood pressure and pulse rate of a group of hypotensive individuals, comparing the results with those on normal adults. From these results, which are to be discussed in detail, a classifica-

tion of hypotension has been ventured as secondary, essential and primary hypotension.* In order to determine whether or not children responded in a manner similar to normal adults, like observations were made on a group of normal children.

Procedure. Changes in blood pressure and pulse rate were noted in three positions: (1) the horizontal, (2) at an angle of 135 degrees and (3) in the vertical. The observations were made at the same period each day, between 2 and 4 p.m. The blood pressure cuff was applied to the right arm and the same mercury column instrument, kept approximately at the level of the patient's heart, was used in every determination. The readings in adults were taken while the patient was on a motor-driven Roentgen ray table. The technique of the procedure was explained in detail to each subject in order to minimize the psychic factors. The observations were started in the horizontal position, allowing sufficient time to elapse until two consecutive readings agreed both as to the pulse rate and blood pressure, thereafter at least 2 minutes were allowed for each change of position.

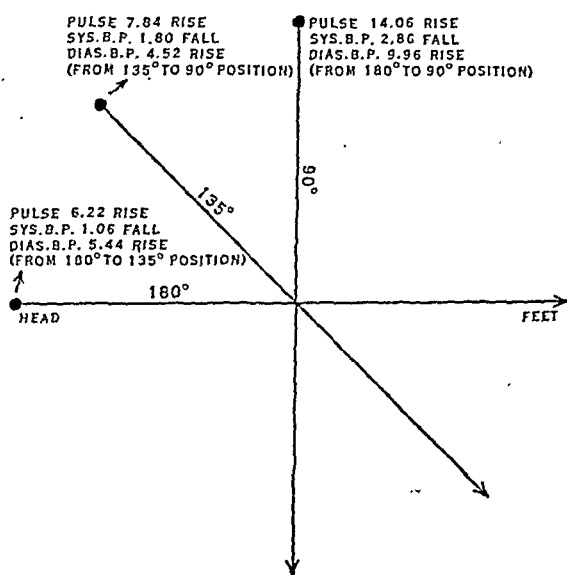


Fig. 1.—Normal adults.

In the children's group the same general principles were carried out except that the Roentgen ray table was not used, as the psychic factors particularly fear and nervousness could not be controlled. The observations were made in the horizontal, sitting and standing positions, using an

* In some instances the terms "essential" and "primary" hypotension have been used synonymously. As classified in this article the terms are not synonymous. "Essential hypotension" is here used to designate those cases of low blood pressure in which no cause can be found but which respond normally to postural change. "Primary hypotension" is here used to describe a distinct group of cases, the symptoms of which are of primary importance and in which the response to change in posture is abnormal. Because this latter group presents definite findings, and may even be considered a distinct entity, the introduction of the term "primary hypotension" for these cases is justified.

ordinary school bench for the determination of the horizontal position. A special blood pressure cuff, 9 cm. wide, was used in the place of the ordinary cuff. In order to obtain an accurate diastolic reading it was found necessary to keep the arm slightly bent at the elbow rather than straight. The following table and figures show the results obtained.

Normal Adults. This group consisted of a series of 50 cases, 25 men and 25 women, the ages ranging from 18 to 64 years, the average age being 30+.

Comment. These results showed that the normal response to interrupted changes in posture from the horizontal to the upright position were a slight fall in the systolic pressure, a rise in the diastolic pressure and a rise in the pulse rate. This rise in pulse rate and rise in diastolic pressure may be explained as follows: in order to overcome the hydrostatic effect of gravity in the upright position, the cardiac rate is increased, also in like manner a vaso-pressor response takes place in the peripheral circulation, which produces a sufficient rise in the diastolic pressure to preclude the possibility of a cerebral anemia.

Normal Children. This group consisted of a series of 60 cases, 30 boys and 30 girls, between the ages of 8 and 10, the average age being 8+. The average height of 52.14 inches and weight of 63.38 pounds for the age were found to be within normal limits.

Comment. When it was noted that the findings on normal adults agreed with those of other observers it was considered necessary to study a group of normal children because it had been rather generally stated that the response in them was different from that in normal adults. Seham and Seham,¹⁸ in 1923, reported findings relative to postural changes in children and stated that: "Comparing the systolic and diastolic pressures in the three postures, one finds that the blood pressure in the lying position is invariably higher than that in the sitting position, and that in the sitting position is practically always higher than that in the standing position." From a study of their tables it was noted that on change of posture from the horizontal to the upright position, a fall in both systolic and diastolic pressures with a rise in the pulse rate occurred.

The results obtained in the present study as shown in Table 1 corresponded in all respects with the group of normal adults. From the horizontal to the sitting position there was a fall in the systolic blood pressure of 0.83 points with a rise in the diastolic blood pressure of 4.36 point, and a rise in the pulse rate of 6.89 points. From the sitting to the standing position the response was a fall in the systolic blood pressure of 1.67 points with a rise in the diastolic blood pressure of 3.64 points and a rise in the pulse rate of 7.11 points. From the horizontal to the standing position the response was a fall in the systolic blood pressure of 2.5 points with a rise in the diastolic blood pressure of 8 points and a rise in the pulse rate of 14 points. As mentioned above, these findings agree

TABLE 1.—THE EFFECTS OF POSTURE ON BLOOD PRESSURE AND PULSE RATE ON A SERIES OF 60 NORMAL CHILDREN.

Blood pressure and pulse rate.														
No of cases.	Age.	Sex.	Height in inches.	Weight in pounds.	Horizontal.			Sitting.			Standing.			
					Systolic.	Diastolic.	Pulse.	Systolic.	Diastolic.	Pulse.	Systolic.	Diastolic.	Pulse.	
14	8	M	* (53.25-48.25) 450.70	(74.50-40.00) 58.98	(110-96) 107	(80-62) 68.71	(106-76) 89	(114-100) 107.42	(82-66) 73.14	(112-84) 96.28	(114-96) 104.28	(86-70) 77.42	(118-90) 101.50	
11	9	M	(59.25-47.50) 52.25	(86.50-52.25) 65.02	(118-94) 108.18	(70-60) 66.18	(96-66) 79.27	(122-100) 108.18	(80-64) 72.72	(100-72) 85.09	(116-94) 105.81	(84-70) 76.18	(108-80) 93	
5	10	M	(58.50-52.50) 55.70	(81.00-63.00) 69.45	(122-94) 111.20	(76-64) 72	(90-68) 74.80	(120-94) 111.20	(80-70) 76.40	(105-76) 84.60	(118-96) 111.20	(86-76) 82	(112-84) 94	
10	8	F	(55.00-48.50) 51.53	(68.75-54.25) 59.25	(122-96) 107.25	(78-62) 69.75	(100-70) 87.87	(118-96) 105.25	(80-64) 73.25	(108-76) 94.75	(124-92) 103.50	(84-68) 76	(112-82) 101.87	
12	9	F	(56.50-49.50) 52.93	(119-53.50) 69.95	(122-100) 109.66	(74-60) 68.83	(96-72) 86.66	(120-100) 108.16	(78-66) 72.33	(104-78) 92.83	(116-100) 108.16	(82-70) 75.83	(114-88) 100.83	
2	10	F	(53.75-52.00) 52.87	(65.50-51.50) 63.50	(118-102) 110	(68-68) 68	(80-78) 79	(114-100) 107	(72-72) 72	(88-84) 86	(110-102) 106	(76-74) 75	(96-86) 91	
460	8.61	..	52.14	63.38	108.26	68.80	84.93	107.43	73.16	91.82	105.76	76.80	98.93	
													† Average.	
													† General average.	
* Figures in parentheses represent the high and low for each group.														

* Figures in parentheses represent the high and low for each group.

† General average.

‡ Average.

closely with those of normal adults both as to fall in systolic pressure, rise in diastolic pressure and rise in pulse rate. From this study it seemed that body build, height and weight in themselves exert no particular influence on blood pressure; however, age and sex seem to play a minor rôle, the blood pressure increasing slightly with age and being somewhat higher in the male. With advance in age in both sexes there was noted a corresponding decrease in the pulse rate.

Secondary Hypotension. This group consisted of a series of 50 cases, 19 men and 31 women, the ages ranging from 18 to 56 years, the average age being 28+.

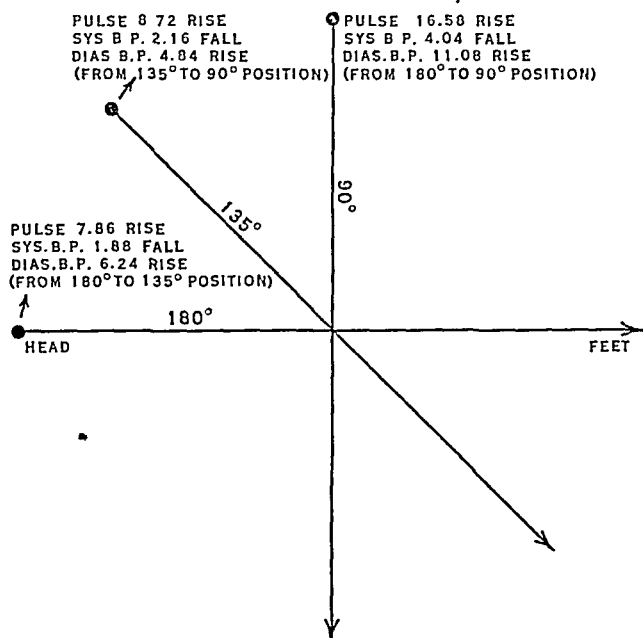


FIG. 2.—Secondary hypotension.

Comment. In all the hypotensive groups a systolic blood pressure of 100 or less taken in the sitting position served as a basis for the diagnosis of hypotension. In this particular group the hypotension was secondary to syphilis in 47 cases and to tuberculosis in 3 cases. In no case in this group were there any symptoms referable to low blood pressure. The results relative to postural change were essentially the same as in the group of normal individuals with the exception that the fall in the systolic pressure, rise in the diastolic pressure and rise in the pulse rate were slightly greater.

Essential Hypotension. This group consisted of a series of 16 cases, 6 men and 10 women, the ages ranging from 21 to 41 years, the average age being 27+.

Comment. This group comprised individuals who accidentally were found to have a low blood pressure. In no case in this group

were there any symptoms referable to the blood pressure and on physical examination nothing could be found which might be responsible for the hypotension. The term essential hypotension is therefore used to denote a low blood pressure without any apparent basis for its existence. The results obtained in this group showed a normal response to posture.

From this it seems safe to state that in a hypotensive individual responding normally to postural change, without symptoms, and without finding any organic lesion to account for the low blood pressure the condition should be considered physiologic. Friedländer¹¹ states that Fisher, of the Northwestern Mutual Life Insurance Company, found in their series of hypotensive persons that

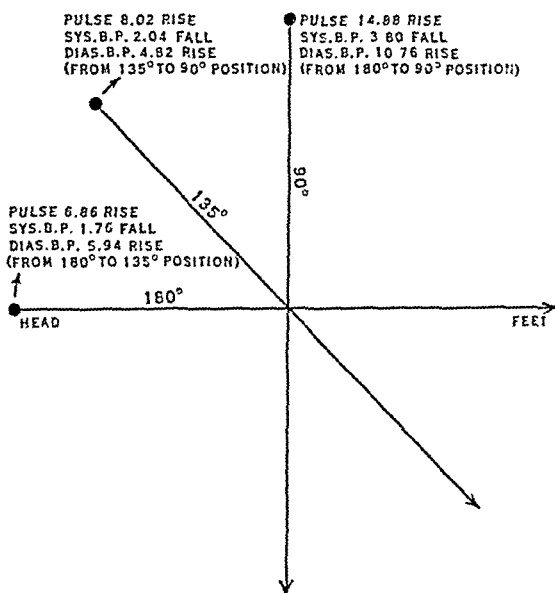


FIG. 3.—Essential hypotension.

the death rate was only 35% of the expected mortality, as contrasted with a general mortality of 80%. Also that Muhlberg, of the Union Central Life Insurance Company, found that a low blood pressure unassociated with any organic lesion in persons past fifty years of age was the best indication that the person would outlive his expectancy.

Primary Hypotension. This group consisted of a series of 7 cases, 5 men and 2 women, the ages ranging from 23 to 52 years, the average age being 31+.

Comment. In each case of this group there were symptoms relative to the low blood pressure: exhaustion, fatigue, lack of endurance and obscure headaches. The symptoms relative to posture

were dizziness and faintness, especially in the standing position: these were less marked but still present in the sitting position.

The results obtained in this group were a decided fall in both the systolic and diastolic pressures, and only a moderate rise in the pulse rate. In a majority of the cases the pulse rate varied little, if any, with change in posture, however in 2 of the cases the pulse rate was markedly increased. These findings are entirely at variance from the normal response to postural change. The reason for this variance might be due to one of the following factors: (1) A hypofunctioning of the constrictor fibers of the vasomotor mechanism producing splanchnic dilatation, (2) a capillary stasis in the splanchnic and pelvic viscera and (3) according to Dale⁸ and others,^{7,9} as quoted by Friedländer,¹⁰ the liberation of a histamine-like substance acting as a chemical poison producing capillary dilatation.

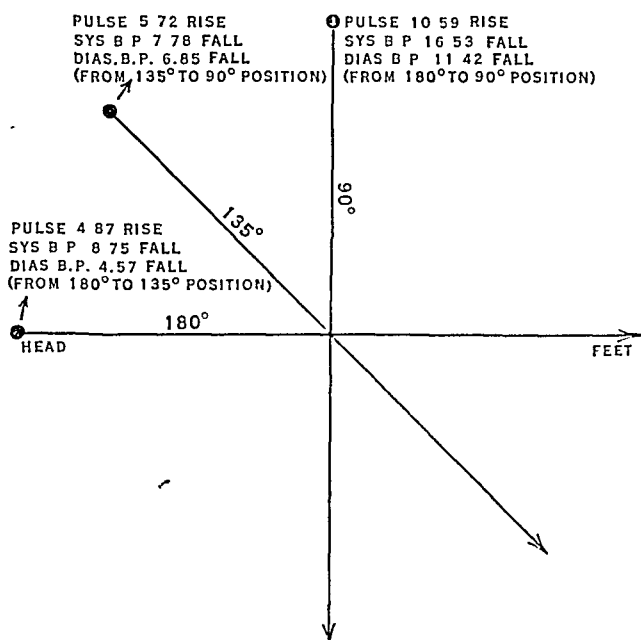


FIG. 4.—Primary hypotension.

Discussion. Thus in normal adults a slight fall in the systolic and a rise in the diastolic pressure and pulse rate occurred in changing from the horizontal to the upright position. The two rises tend to overcome the hydrostatic effects of gravity in the upright position, thereby precluding weakness and dizziness which would be the manifestations of a cerebral anemia. A similar study made on normal children showed similar findings.

Among hypotensive individuals (a systolic blood pressure of 100 or less in the sitting position), the secondary hypotension cases responded in a normal manner. This particular group had either

syphilis or tuberculosis. No symptoms were complained of and no treatment was given for the symptom of hypotension, the treatment being directed solely toward the underlying process.

The essential hypotension cases were so designated because no apparent reason could be found for the hypotension. This group presented no symptoms whatever relative to the hypotension, and responded in a normal manner to change in posture.

The primary hypotension group however presented entirely different findings. In the first place, all responded abnormally to postural change, a marked drop in both systolic and diastolic pressures occurring with very little increase in the pulse rate. In the second place, all patients in this group presented symptoms referable to the blood pressure on change of posture, these being principally dizziness and faintness especially when in the upright position. In addition to the symptoms referable to blood pressure, the members of this group complained of fatigue, of tiring easily on exertion and of frequent headaches. The reason for the abnormal response to posture might be a hypofunction of the vasoconstrictor mechanism causing a dilatation of the splanchnics. Capillary stasis in the splanchnics and pelvic viscera or vasodilatation due to liberation of a histamine-like substance should be considered a possibility. The symptoms of dizziness and faintness in the upright position were probably the result of a varying degree of cerebral anemia.

Because the response to postural change in the primary hypotension group was similar to that of the condition described by Bradbury and Eggleston⁵ as "postural hypotension," it might be well to consider this group as mild cases of "postural hypotension." The symptomatology of the two conditions is similar and the cardinal symptoms differ only in degree. As to whether or not cases which are here designated as primary hypotension, if untreated and allowed to progress, would finally become cases of true postural or orthostatic hypotension is worthy of consideration. The etiology of the two conditions, primary hypotension and "postural hypotension," although unknown, is very likely the same, being primarily a faulty vasomotor mechanism.

Further evidence as to the similarity between primary hypotension and "postural hypotension" may be found in the response to treatment. Ghrist¹² and others^{1,2,3,17,20} have shown that benefit is derived from (1) the oral administration of ephedrine sulphate, and (2) the application of a snugly fitting abdominal binder. These same measures have been found to be of considerable aid in cases of primary hypotension. The fact that both conditions respond to ephedrine sulphate gives additional information as to the etiology, for according to Bastedo,⁴ ephedrine in average sized doses is a sympathetic stimulant, acting peripherally and for the most part on the myoneural junctional tissues. The physiologic effects are

those of cardiac acceleration and vasoconstriction bringing about an increased heart rate and a rise in blood pressure, the greatest vasoconstriction taking place in the vessels of the splanchnic area where probably the effect is most needed. From this it seems that a depression of the myoneural junctional tissues, particularly in the splanchnic vessels, might be responsible for the hypofunctioning of the vasoconstrictor mechanism.

In consideration of the above the following descriptive classification of hypotension is presented:

CLASSIFICATION OF HYPOTENSION. 1. Physiologic: Essential hypotension.

2. Pathologic: (a) Primary hypotension (circulatory) (disturbed vasomotor mechanism); (b) secondary hypotension (non-circulatory) (secondary to acute infectious diseases, chronic debilitating diseases as syphilis, tuberculosis, etc.).

In every patient with hypotension or in patients presenting symptoms of dizziness and feeling of faintness the postural test for circulatory efficiency should be made by taking the blood pressure in more than one position, preferably in all three, the horizontal, sitting and standing. This test is a very simple procedure, entails no elaborate equipment, an ordinary examining table being sufficient, takes little time and may give valuable information. A slight fall in the systolic pressure, a rise in diastolic pressure and a rise in the pulse rate constitute a normal response to postural change and places the particular case of hypotension in either the essential or secondary groups. These groups need no particular treatment relative to the blood pressure. A decided fall in both the systolic and diastolic pressure with little, if any, rise in the pulse rate constitutes an abnormal response and places the case in the primary or postural hypotension group. These cases have such prominent symptoms relative to the blood pressure, that treatment should be instituted.

Conclusions. 1. There is presented a study of the effects of posture on the blood pressure and pulse rate in normal adults, normal children and a group of hypotensive individuals classified as secondary, essential and primary hypotension.

2. The response in the normal groups to postural change from the horizontal to the upright position was a slight fall in the systolic blood pressure, a definite rise in the diastolic blood pressure and a rise in the pulse rate. In the secondary and essential hypotension groups a similar response was noted. The primary hypotension group, however, responded abnormally by manifesting a decided fall in both the systolic and diastolic blood pressures with only a slight increase in the pulse rate.

3. The similarity between primary hypotension and "postural hypotension" is suggested.

4. A test for circulatory efficiency and vasomotor stability has

been outlined, and as a result of this test a classification of hypotension is presented.

Thanks are due Dr. O. C. Wenger and Dr. J. R. Waugh for permission to study certain cases, and to Dr. Clyde Brooks and Dr. Paul S. Carley for valuable suggestions.

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CHRONIC MENINGOCOCCUS SEPTICEMIA.

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CHRONIC meningococcemia, unaccompanied by meningitis or with meningitis occurring usually as a late complication, can no longer be regarded as a rare clinical entity. Many cases have undoubtedly gone unrecognized. During the past few months there has been a noticeable rise in the incidence of this condition in New York City. This is not unusual preceding or following an outbreak of meningococcal meningitis.

Since its first description by Soloman,² in 1902, chronic meningococcus septicemia has been a subject of great interest to many investigators. As pointed out by Harrison and Abernethy,³ Dock,⁴ and Binns and Fothergill,¹ this interest was until recently largely confined to foreign writers, especially those of the French and German schools. Recently, however, reports in the American literature have become more frequent.

In this paper no effort will be made to review this literature, as my object is simply to present the outstanding clinical and laboratory features that have developed in the study of a group of 15 cases of chronic and subacute meningococcemia.

As shown in Table 1, the disease attacks males and females with about equal frequency. It will be noted also that the disease may occur at practically any age, the youngest in this series being 3 and the oldest 52 years.

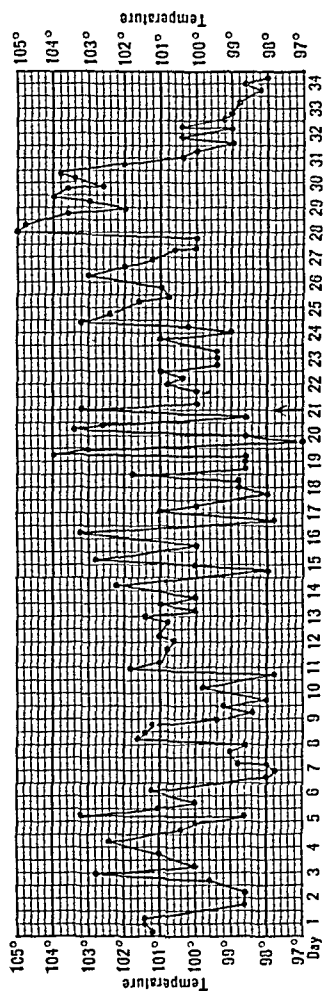


FIG. 1.—Temperature chart in Case 11. Arrow indicates when serum treatment was begun.

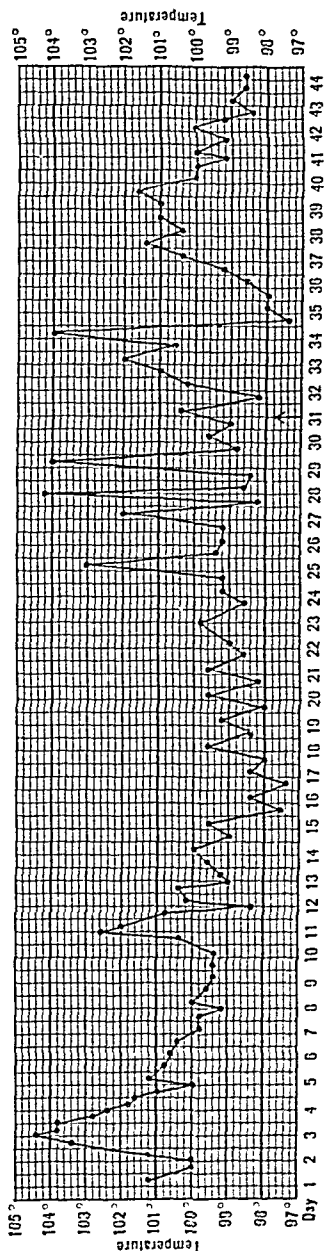


FIG. 3.—Temperature chart in Case 12. Note the afebrile periods. Arrow indicates when serum treatment was begun.

Symptomatology. The disease is usually characterized by a rather sudden onset, with headache, fever, joint pains and skin eruption. Chills or chilly sensations are common. At times the disease is ushered in by a severe tonsillitis or some other upper respiratory infection. Occasionally meningitis may inaugurate the illness. In rare instances there is a slow insidious onset with an irregular fever.

TABLE 1.—CLINICAL DATA.

Case.	Sex.*	Age, yrs.	Symptoms.	Complications.	Duration, wks.	Treatment.	Result.
1	♀	3	Fever, arthralgia, purpuric rash	Meningitis, 4th week nephritis	5	Serum intraspinally; autogenous vaccine	Recovered.
2	♀	40	Headache, chills, fever, maculopapular rash	Meningitis, 6th week	7	Serum intraspinally; serum intravenously, 3 doses of 50 cc.	Died.
3	♂	10	Chills, fever, polymorphous rash	Nephritis, endocarditis	7	Serum intravenously, 6 doses of 40-60 cc.	Recovered.
4	♀	48	Headache, chills, fever, arthritis, maculopapular rash	Endocarditis	7	Serum intravenously, 1 dose 20 cc.; serum intramuscularly, 10 doses of 20 cc.	Recovered.
5	♀	8	Fever	Meningitis, 7th week	8	Serum intraspinally; serum intravenously	Recovered.
6	♀	13	Headache, fever, arthralgia, maculopapular rash	Meningitis, 6th week	7	Serum intraspinally; serum intravenously	Recovered.
7	♂	29	Headache, chills, fever, arthralgia, purpuric rash	3	Serum intravenously, 5 doses of 30 cc.	Recovered.
8	♂	28	Headache, fever, herpes	3½	Serum intravenously, 7 doses of 80 cc.	Recovered.
9	♂	31	Headache, fever, arthralgia, maculopapular rash	Epididymitis	7	Serum intraspinally; serum intravenously, 4 doses of 20 cc.	Recovered.
10	♂	52	Headache, chills, fever, arthralgia, maculopapular rash	Meningitis, 14th week	17	Serum intraspinally; serum intravenously, 6 doses of 80 cc.	Died.
11	♀	19	Headache, chills, fever, arthralgia, polymorphous rash	Endocarditis; myocarditis?	5	Serum intravenously, 4 doses of 100 cc., 1 dose of 200 cc.	Recovered.
12	♂	35	Headache, chills, fever, tonsillitis, arthralgia, arthritis, polymorphous rash	Epididymitis	5½	Serum intravenously, 3 doses of 100 cc., 2 doses of 150 cc.	Recovered.
13	♀	23	Headache, chills, fever, arthralgia, polymorphous rash	Meningitis, 1st week	13	Serum intraspinally; autogenous vaccine	Recovered.
14	♂	20	Headache, chills, fever, arthritis, polymorphous rash	Meningitis, 2d week; endocarditis?	18	Serum intraspinally	Recovered.
15	♂	3½	Headache, fever, polymorphous rash	4	Serum intravenously, 6 doses of 40 cc.	Recovered.

* In this column, ♂ denotes male; ♀, female.

The fever is of the intermittent type (Fig. 1), ranging from 99° to 103° or 104° F., and continues as such throughout the course of illness, at times with afebrile periods of 2 to 10 days (Fig. 3). The temperature curve often has a superficial resemblance to malaria, and indeed, may occasionally present tertian or quartan paroxysms. The rises in temperature are frequently accompanied by chills or chilly sensations.

Joint manifestations are very common (Table 1). These are usually in the form of migratory arthralgias, although actual swelling and tenderness of joints are fairly frequent. A suppurative arthritis is relatively uncommon, and is as a rule monoarticular, involving most frequently one of the knee joints. The joint symptoms are a prominent feature early in the course of the disease but may recur in the later stages.

The skin rash is perhaps the most striking feature of the disease.

It appears usually during the first week, but may occur at any stage of the illness. The lesions vary in type, size, and extent of distribution. In some of the cases I have been able to distinguish 6 or 7 types of lesion (Figs. 2 and 4). There were faint pink to deep red macules, fading on pressure and in size ranging from 0.25 to 2 cm. in diameter. There were papules, which showed similar variations in color and size; some were indurated and tender, resembling the eruption of erythema nodosum. There were petechial and larger hemorrhagic lesions. There was an interesting lesion consisting of a pin-head-sized hemorrhage surrounded by a macular areola. The most distinctive lesion was an irregularly round



FIG. 2.—Skin eruption in Case 11. The hemorrhagic lesions are quite distinct. The maculopapular lesions appear very faint.

hemorrhage with a bluish-gray center, which contained pus cells. In 2 other cases not included in this study I have seen raised pustules. A case with a pustular eruption was reported also by Harrison and Abernethy.³ Herpes was observed in 2 instances.

The eruption is usually maculopapular or polymorphous (Table 1). Only one type of lesion may be present. Rarely there may be no skin eruption. Not infrequently the character of the eruption changes during the course of the disease. The rash may be localized or very diffuse. The lesions tend to disappear after several days and then recur. Frequently new crops come out with each rise of temperature and those may last only 12 or 24 hours. Sub-

conjunctival and other mucous membrane hemorrhages are occasionally present.

In the uncomplicated case there are no other remarkable physical signs, except that there may be some enlargement of the spleen. It should be emphasized, however, that as a rule the patient does not appear very toxic or acutely ill. Indeed, it seems extraordinary that in spite of an apparently severe sepsis the patient's general condition remains quite good.



FIG. 4.—Skin eruption in Case 12. The hemorrhagic lesions are very prominent. The maculopapular lesions are indistinct.

Complications. The most important and frequent of the complications is meningitis. In this series it occurred in 7 instances, an incidence of 46.6%. It is usually a late complication (Table 1), but may occur early or even at the onset of the disease. In 2 instances the meningitis relapsed once or twice. The meningeal infection usually responds to specific serum therapy. In this study 5 of the 7 patients with meningitis recovered. It would seem that the presence of this complication does not as a rule make the outlook more serious. Certain workers, notably Chaler, Giraud and Morel,² even believe that the localization in the meninges aids in the control of the general infection.

The literature supplies ample evidence that the meningococcus is a cause of endocarditis.⁷ However, the frequency and prognostic significance of this complication in meningococcemia are matters of controversy. While certain investigators are of the opinion that it is relatively uncommon and almost invariably fatal, others believe

that it is frequently present, and even indicate that the endocardial lesion may be the source of infection in many cases, and that many patients with this lesion make a complete recovery.

During the course of the disease it is often difficult, if not impossible, to determine with any degree of certainty the presence of an endocardial lesion. It is well known that an endocarditis may be present without any clinical evidence, and that the presence of even a harsh murmur is not a sure indication of organic endocardial involvement.

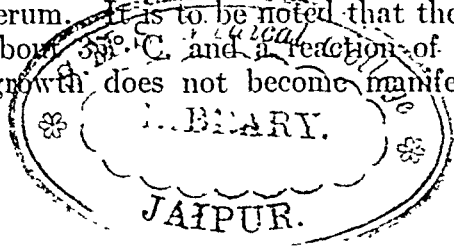
In this study the diagnosis of endocarditis was based on the development of an endocardial murmur or murmurs, particularly if diastolic, which persisted throughout the course of illness, on the presence of clinical or electrocardiographic evidence of impaired myocardial function, and on the roentgenographic changes in the size and contour of the heart, particularly during convalescence. A progressive rise in the number of bacterial colonies in the blood culture during the active phase of the disease was regarded as corroborative evidence of endocardial infection.

Endocarditis was regarded as definitely present in 3 instances (Table 1). In 1 of these there was probably an associated myocarditis. There was 1 case with a suspected endocardial lesion. It is to be noted that all the patients with endocarditis recovered. It would seem, therefore, that endocarditis is not an infrequent complication of meningococcus septicemia, and that the prognosis in such patients is not necessarily grave.

The occurrence of nephritis as a complication of meningococcemia is rather unusual. In this series there were 2 instances of nephritis, which were of the acute or subacute glomerular type. Both patients recovered. Cases with nephritis were reported also by Warfield and Walker,⁷ and by Harrison and Abernethy.³

Another remarkable and not infrequent complication is epididymitis. Two of the patients in this series presented this complication, which cleared up in 6 or 7 days. I have seen infections of the epididymus in 2 other cases of meningococcemia not included in this study. In a recent report of 26 cases of epidemic meningococcus meningitis, Tillett and Brown⁶ found 2 instances of epididymitis.

Laboratory Data. It is apparent that the diagnosis of meningococcus septicemia may be suspected on clinical grounds. However, for an absolute diagnosis it is essential to recover the organisms from the blood stream. This is not always an easy matter, and indeed, repeated blood cultures are often necessary before a positive result is obtained. It is advisable to take the culture when the patient is having a rise in temperature and to use 5 to 10 cc. of blood. The medium should consist of good nutrient broth, preferably enriched with ascitic fluid or blood serum. It is to be noted that the meningococcus grows best at about 37° C. and a reaction of 7.2 to 7.4 pH. Very often the growth does not become manifest for



several days. It is important, therefore, to incubate the cultures for 7 to 10 days before discarding them as negative. Without transplants the culture as a rule remains alive but a short time. Sometimes it is difficult to obtain subcultures. The organisms may remain alive for a number of weeks on semisolid media containing 1% glucose and from 0.25 to 0.5% agar. It is interesting to note that blood cultures taken early in the disease most frequently reveal no growth. In the majority of the cases a positive blood culture was not obtained before the third week of the illness (Table 2).

TABLE 2.—LABORATORY DATA.

Case.	White blood cells.	Poly-morpho-nuclears.	Week of illness when first positive blood culture.	Other findings.
1	1	Spinal fluid shows typical findings of meningitis.
2 . . .	8,400	80		Spinal fluid shows typical findings of meningitis.
	12,000	83	4	
3 . . .	28,000	91	6	
4 . . .	17,000	76	4	
5	Not given	Spinal fluid shows typical findings of meningitis.
6 . . .	14,600	80	5	Spinal fluid shows typical findings of meningitis.
7 . . .	12,500	87	2	Spinal fluid normal.
8	Early	
9	Not given	Spinal fluid normal.
10 . . .	27,000	81	14	Spinal fluid normal at first; 14 days later showed findings of meningitis.
	21,500	88		Nasopharyngeal culture negative for strain, men-
11 . . .	8,400	62	3	ingococci; erythrocyte sedimentation rate, 40 mm. in 1 hour.
	13,000	89		Nasopharyngeal culture negative for meningococci; serum agglutinated slightly his own strain, but not other meningococci; prostatic smear neg. for gonococcus; gonococcus complement-fixation test, neg.; Felix-Weil reaction neg.; several biopsies of skin lesions neg. for meningococci; spinal fluid normal.
	31,200	91		Serum did not agglutinate meningococci; spinal fluid, normal at onset, 5 days later showed findings of meningitis.
12 . . .	22,000	90	4	Spinal fluid showed findings of meningitis.
	36,000	91		Spinal fluid essentially normal.
	10,000	72		
	32,000	91		
13 . . .	14,000	87	7	
14 . . .	20,000	86	9	
	25,000	90		
15	1	

For the proper identification of the organism one must resort to sugar fermentation and agglutination tests. It is to be noted that different strains of meningococci vary much in their agglutinability. Certain investigators have pointed out that prolonged incubation may disturb the specificity of agglutination.

In the literature on meningococcemia there are frequent references to the agglutinative properties of the patient's serum. In Cases 11, 12 and 13 the serum failed to agglutinate meningococci (Table 2). Furthermore, in Cases 11 and 12 the causative strain was only slightly agglutinated by the patient's own undiluted serum. In 2 other cases, not included in this study, I have obtained similar negative results. Harrison and Abernethy³ reported a similar

experience. In a group of 12 recovered meningococcic meningitis cases, Neal⁴ was unable to obtain agglutination of meningococci with the serum of any of the patients. The impression gained from this study is that in meningococcus infection agglutinin production is very limited, and that this antibody plays a very small rôle in the immunity mechanism in this disease.

Several nasopharyngeal cultures in Cases 11 and 12, as well as in 2 other cases not included in this study, were negative for meningococci. Likewise, several biopsies of skin lesions failed to show the organisms.

There is nothing remarkable about the blood count. There is usually a leukocytosis ranging from 10,000 to 36,000 (Table 2). The percentage of neutrophils is usually between 80 and 90. It is to be noted that the leukocyte count may vary considerably during the course of the disease.

The spinal fluid in the cases unaccompanied by meningitis was normal. The cases with meningitis showed the typical spinal fluid findings of meningococcic meningitis. Some workers have cautioned against doing a spinal tap in the absence of definite signs of meningitis because of the danger of localization of the infection in the meninges. This, however, is not borne out by the present study. Meningitis did not develop in Cases 7, 9, 12 and 15 following lumbar puncture (Table 2). In Case 10 there was an interval of 2 weeks and in Case 13, 5 days between the spinal tap and the occurrence of meningitis. It seems to me that the relationship between the spinal tap and the meningeal involvement is very doubtful, if not improbable, in Case 10, and uncertain in Case 13. My belief is that a spinal tap should certainly be performed if any signs of meningeal irritation are present.

Differential Diagnosis. The diseases with which chronic meningococcemia may be confused are rheumatic fever, malaria, typhoid, subacute bacterial endocarditis, miliary tuberculosis, Brill's disease, Malta fever, gonorrheal sepsis, measles, erythema multiforme, erythema nodosum and secondary syphilis.

Course. The average duration in untreated cases of chronic meningococcemia is several months. The duration is markedly shortened in the treated cases, particularly if the diagnosis is established early. The shortest duration in this series was 3 weeks and the longest 18 weeks. The latter was an untreated case (Table 1).

In order to illustrate the clinical course the following 3 cases from this series are recited in detail:

Case Reports. CASE 11.—A. M., a girl, aged 19, admitted to Bellevue Hospital, November 1, 1935, complained of pain in both legs, arms and back and of a burning skin eruption. The onset of these symptoms was rather sudden, 4 days prior to admission. The past history was negative except for the removal of a breast tumor 5 years ago.

The patient was well nourished and did not appear acutely ill. A diffuse eruption was present over the face, neck, chest, abdomen, arms, legs, hands and feet (Fig. 2). It consisted of erythematous blotches and nodules, varying in size from 2 mm. to 2 cm. in diameter. Many of the lesions were purpuric, particularly those over the hands and feet. There was a hemorrhagic lesion on the upper lip. The pharynx was slightly congested. The heart beat was regular and moderately rapid, with sounds of good quality. A blowing systolic murmur was heard over the apex and mitral regions. The lungs were clear. The spleen was not felt. There was tenderness over both knee joints. The fundi were normal. The reflexes were normal, and there were no signs of meningeal irritation. The temperature was 101° F., the pulse 98 and the respiration 24. The white blood count showed 8400 cells with 62% neutrophils. The erythrocyte sedimentation rate was 40 mm. in 1 hour. Blood cultures taken on November 5 and 9 were both sterile. The diagnosis at this time was acute rheumatic fever.

Although the patient remained fairly comfortable, the fever continued (Fig. 1). It would drop to 98° or 99° F. in the morning and rise to 102° or 103° F. in the afternoon. The polymorphous eruption would fade, only to be followed by a new crop of lesions. The diagnosis of meningococcemia was now suspected. On November 14, a blood culture, taken on ascitic broth, was positive for meningococci. A blood culture taken on November 20 showed an increasing number of bacterial colonies. A nasopharyngeal culture was negative for meningococci. The white blood count was now 31,200 with 91% neutrophils. The patient's serum did not agglutinate meningococci. The causative strain of meningococcus was only slightly agglutinated by her serum.

On November 21, serum treatment was begun. For 5 days she received a daily intravenous injection of 100 cc. of antimeningococcic serum, diluted with normal saline solution. The sixth dose consisted of 200 cc. of the serum.

November 23, a severe serum reaction occurred in the form of a diffuse urticarial and erythematous rash and a generalized adenopathy. This reaction, while somewhat relieved by repeated small doses of adrenalin, persisted for about a week. Since the blood cultures remained positive and showed a progressively increasing number of bacterial colonies, it was deemed wiser to continue the serum therapy in spite of the reaction. Simultaneously with the recession of the serum reaction the patient's temperature dropped to normal, and the blood culture became sterile.

When the patient was allowed out of bed, on December 9, she had an attack of dyspnea. Examination of the heart showed that the apical murmur became harsher and that the second pulmonic sound became accentuated. The electrocardiogram showed a sinus tachycardia and a partial A-V block. The roentgenogram depicted a roughly pyriform heart with accentuation of the right auricular curve and a steep left border, suggestive of early mitral stenosis. These findings were still present at the time of her discharge from the hospital, on December 30. It was felt that this patient had an endocarditis and probably also a myocarditis.

CASE 12.—E. T., a man, aged 35, admitted to Bellevue Hospital, November 7, 1935, complained of headache, chills and fever, sore throat, pains in the calves of his legs and right ankle. The onset of these symptoms was about 24 hours prior to his admission. The family history revealed that his wife died 24 hours ago of a fulminating form of meningitis after a brief illness of 4 days.

Physical examination showed the patient to be well nourished, somewhat apprehensive, but fairly comfortable. The temperature was 101° F., the pulse 120 and the respiration 20. There was marked pharyngeal and

tonsillar congestion with suggestive purpuric blotches on the palate. Except for the rapid rate, the heart was negative. The lungs were clear. The spleen was not felt. There was tenderness over both calves and redness and tenderness over the right ankle. The reflexes were normal and there were no signs of meningeal irritation. A purpuric and faint macular eruption was scattered over his abdomen and extremities. The fundi were normal. The diagnosis of meningococcemia was suspected on admission.

The blood count showed 22,000 leukocytes with 90% neutrophils. The blood culture was sterile. The nasopharyngeal culture was negative for meningococci. The gonococcus complement-fixation test and the Felix-Weil reaction were both negative. A prostatic smear was negative for gonococci. The spinal fluid was clear and showed no abnormal findings.

The temperature rose to 104° F. on November 9 and declined again to 101° F. on November 11, when a crop of fresh skin lesions and also herpes labialis appeared. On this date the patient developed also swelling and tenderness of the right epididymus. This complication cleared up in about 6 days.

For a period of 2 weeks the patient continued to run an irregular fever. This was followed by an afebrile period of 10 days (Fig. 3). At this point the patient was about to be discharged.

On December 2, following the afebrile period, the temperature rose sharply to 103° F. At the same time there appeared a new crop of maculopapular and hemorrhagic skin lesions over the face, chest, abdomen and extremities (Fig. 4). The lesions varied in size from 2 mm. to about 2 cm. in diameter. Some of the papules were indurated and tender, resembling the eruption of erythema nodosum. There were some macular lesions with small hemorrhagic centers, and some hemorrhagic lesions with bluish-gray centers. The left eye showed a subconjunctival hemorrhage. There were also migratory joint pains. The spleen was definitely palpable. A blood culture taken on this date was positive for meningococci 4 days later. Several biopsies of skin lesions were negative for organisms. The patient's serum did not agglutinate meningococci. His own strain of meningococcus was only slightly agglutinated by his serum.

December 7, antimeningococcic serum treatment was begun. The patient received intravenously a daily dose of 100 cc. of the serum for 3 days, and 150 cc. for 2 days. The temperature at this time ranged from 98° to 104° F. Following the last dose of serum the temperature declined abruptly from 104° F. to normal. Likewise, the joint pains and most of the skin lesions disappeared. The blood cultures became sterile.

A severe serum reaction occurred on December 13. There was a rise in temperature accompanied by swelling of the face, diffuse erythema and urticaria and generalized adenopathy. Five days later the serum sickness cleared up, and the patient's temperature became normal. His convalescence was uneventful and recovery was complete.

CASE 13.—S. K., a girl, aged 23, was taken ill suddenly, October 3, 1935, with severe headache, chills and fever of 103° F. Except for slight stiffness of her neck the physical examination was essentially negative. A spinal tap performed on October 4 yielded a clear fluid which showed no abnormal findings. Her condition remained unchanged until October 8, when she presented definite signs of meningeal irritation. There was marked nuchal rigidity, and positive Brudzinski, Kernig and Babinski signs. The temperature was 105° F., the pulse 100 and the respiration 22. A spinal tap performed on this date yielded 30 cc. of cloudy fluid. After removal of the fluid, 20 cc. of antimeningococcic serum was injected intraspinally. Examination of the fluid showed a large increase in cells, practically all neutrophils, a moderate increase in the protein and a slight diminution in the sugar. No organisms were found on smear or culture.

October 9, the patient's general condition was somewhat better, but a hemorrhagic eruption appeared on the skin. A lumbar puncture was again performed, 45 cc. of cloudy fluid removed, and 20 cc. of antimeningococcic serum injected intraspinally. The fluid findings were practically the same as those of the preceding day.

October 10, there was a marked improvement in the clinical picture, and the temperature dropped to 99° F. The spinal fluid on this date was only slightly hazy, showed 240 cells, mainly neutrophils, moderate increase in the protein, marked diminution in sugar, but no organisms on smear or culture. No serum was given.

October 11, the temperature rose to 104° F., and the patient developed pain and tenderness in the joints of the left foot. The spinal fluid was clear, showed 105 cells, with 70% mononuclears, moderate increase in protein, moderate amount of sugar and no organisms. No serum was given.

The patient felt quite well on October 12 and 13. The temperature was normal. The spinal fluid remained clear.

October 14, the temperature rose again to 103° F. Nuchal rigidity was again present. A spinal tap yielded 30 cc. of hazy fluid, which showed a large increase in cells, mainly neutrophils, moderate increase in protein, a decided drop in the sugar, but no organisms by smear or culture. Twenty cc. of antimeningococcic serum was injected intraspinally.

The following two weeks the patient presented an appearance of well-being, although she continued to run an intermittent fever. During this period 8 spinal taps were performed. The spinal fluid findings were at first similar to those of October 14, but gradually cleared up and became normal. Antimeningococcic serum was injected intraspinally on 4 occasions.

October 29, there appeared a diffuse polymorphous eruption over the trunk and extremities. The lesions consisted of macules, papules, urticarial and purpuric spots.

From this time on the patient continued to run a septic type of fever with a temperature of 99° F. in the morning and 102° to 105° F. in the afternoon. Occasionally there was an afebrile day. Crops of new maculopapular and hemorrhagic lesions appeared again and again, and would fade in a few days. There were also migratory joint pains.

Blood cultures taken on October 18 and on November 14 were both sterile. The patient's serum failed to agglutinate meningococci. The white blood count was 14,200 with 87% neutrophils. A third blood culture taken November 27 was positive for meningococci 5 days later.

In view of the fact that the patient had been sensitized to serum, it was decided to resort to vaccine therapy. An autogenous vaccine was prepared, and used at first subcutaneously and later intravenously. The first subcutaneous injection was given on December 6, and consisted of 100 million bacteria. These treatments were given every second day in increasing doses, the maximum being 2 billion bacteria. After employing the subcutaneous route for about 2 weeks without any striking benefit, the patient was given 3 intravenous injections of the vaccine. The respective doses were 100, 200 and 600 million bacteria. The last treatment was on December 31, and almost immediately the temperature declined from 102° F. to normal. With the subsidence of the fever, the patient progressed satisfactorily to complete recovery.

Prognosis. The prognosis in chronic meningococcus septicemia appears to be favorable, even in the presence of complications. In this series only 2 of 15 patients died, a mortality of 13.3%. Both fatal cases had meningitis. It is to be noted, however, that in 1 of these cases (No. 10) specific treatment was first begun in the fourteenth week of his illness.

Treatment. There is no doubt that some cases of chronic meningococcemia recover spontaneously. However, as previously pointed out, the duration of the illness is markedly prolonged in the untreated cases. The hazards of a prolonged sepsis are well known. It is important, therefore, to check the disease as quickly and as effectively as possible.

From this study and from experience with other cases not included in this series, I am convinced that the disease can be controlled promptly and effectively by the intravenous use of antimeningococcic serum. As pointed out by Binns and Fothergill,¹ failure to respond to specific serum treatment might be due to the use of an inactive serum or perhaps a serum that is not antigenically specific for the strain of meningococcus infecting the patient. It has been suggested also that the presence of a focus of chronic meningococcus infection, such as sinus involvement, may be responsible for certain failures. It is my impression also that the serum is less effective in the late stages of the disease.

The serum was administered intravenously in 12 cases (Table 1). One patient, however, received only 1 intravenous dose followed by 10 intramuscular injections. Of course, patients with meningitis received serum intraspinally as well as intravenously. Treatments were given once daily. The intravenous dose varied from 20 to 200 cc. The total amount of serum used in the individual case varied from 80 to 600 cc.

It is indeed difficult to determine with accuracy the quantity of serum required in each case. It is my impression that it is not necessary to use massive but rather adequate doses of serum. In general, the dosage will vary with the response made by the individual patient. The question of dosage, I believe, merits further study.

The use of autogenous vaccine in the treatment of chronic meningococcus septicemia is at present difficult to evaluate. Vaccine was used in 2 cases with apparent benefit (Table 1). In Case 13 prompt improvement followed the intravenous use of the vaccine. I believe that autogenous vaccine may prove a valuable adjuvant to the serum treatment in certain selected cases of chronic meningococcemia.

Summary and Conclusions. Chronic meningococcus septicemia is a distinct clinical entity, characterized by headache, intermittent fever, migratory joint pains, and the presence of a characteristic maculopapular or polymorphous rash. The patient's general condition appears good. The disease is probably more common than generally suspected.

The outstanding complications are meningitis, endocarditis, nephritis and epididymitis.

The diagnosis may be suspected on clinical grounds. However, for an absolute diagnosis one must obtain a positive blood culture for the meningococcus. Repeated blood cultures are often neces-

sary. It appears that the patient's serum does not as a rule agglutinate meningococci. The spinal fluid in cases unaccompanied by meningitis is normal. There appears to be no danger of localization of the infection in the meninges following spinal tap.

The duration of the disease is several months, but is markedly shortened in the treated cases. The prognosis is as a rule favorable, even in the presence of complications.

The disease responds promptly to the intravenous use of an antimeningococcic serum. Adequate but not massive doses of serum are required. Spontaneous recovery may occur. In certain selected cases the use of an autogenous vaccine may be a beneficial therapeutic measure.

The author desires to express his gratitude to Dr. Josephine B. Neal for valuable suggestions and criticisms.

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BOOK REVIEWS AND NOTICES.

DIE WERKE DES HIPPOKRATES. HERAUSGEGEBEN VON DR. MED. RICHARD KAPFERER unter MITWIRKUNG VON PROF. DR. GEORG STRICKER, Würzburg. Book 7: Die Natur (Konstitution) des Menschen / Die Nahrung / Die Gäste (The Nature (Constitution) of Man), (The Nutriment), (The Humors). Pp. 85. Stuttgart: Hippokrates Verlag G.M.B.H., 1934. Price, Rm. 7.50. (To be published in 25 parts costing *ca.* Rm. 100, card binding.)

In the book on "The Nature of Man," supposed to have been written by Hippocrates' son-in-law, Polybos, the Editor points out how the apparent miscellany of the last six chapters really has a logical connection with the earlier exposition of humoral pathology. The book on "Nutriment," including in the term the utilization as well as the introduction of nourishing solids, liquids and gases, has caused obvious difficulties to the translator that have not been entirely overcome. Incomplete sentences and cryptic expressions almost conceal the identity of thought with other Hippocratic writings. In "The Humors," accepted by Erotian as a true work of Hippocrates, the humoral doctrine is applied to many disorders of various parts of the body and appropriate therapy deduced on an allopathic basis.

E. K.

PRESCRIPTION WRITING AND FORMULARY. The Art of Prescribing. By CHARLES SOLOMON, M.D., Assistant Clinical Professor of Medicine, Long Island College of Medicine; Associate Attending Physician and Chief of the Medical Clinic, Jewish Hospital of Brooklyn, etc. With a Foreword by LEWELLYS F. BARKER, M.D. Pp. 351; 32 illustrations. Philadelphia: J. B. Lippincott Company, 1935. Price, \$4.00.

THIS book is full of useful and practical information that should recommend it highly to students and young physicians. Its availability would however, be greatly enhanced if it were printed on thin paper and bound in a flexible cover, so that it could be conveniently carried in a pocket or handbag.

R. K.

A GUIDE TO HUMAN PARASITOLOGY. By D. B. BLACKLOCK, M.D. (EDIN.), D.P.H. (LOND.), D.T.M. (LIVER.), Professor of Tropical Hygiene, Liverpool School of Tropical Medicine, the University of Liverpool, and formerly Professor of Parasitology; Director of the Sir Alfred Lewis Jones Laboratory, Freetown, Sierra Leone, West Africa, and T. SOUTHWELL, D.Sc., PH.D., A.R.C.Sc., F.Z.S., F.R.S.E., Walter Myers Lecturer in Parasitology, School of Tropical Medicine, The University, Liverpool, etc. Pp. 259; 122 illustrations and 2 colored plates. Second edition. Baltimore: William Wood & Co., 1935. Price, \$4.00.

In the second edition of this book, sections on vein, organ and spinal puncture, on therapy and on some of the rarer parasites of man have been deleted. Occasional paragraphs have been added and some illustrations improved. While these changes do not alter materially the value of the book, its utility is lessened by omitting the chapter on treatment. The few pages originally given this subject may have been inadequate, but some amplification of the text, if supported by reference to easily available treatises, would certainly be valuable to the class of students for whom the book is intended.

H. R.

FOLK-LORE FROM ADAMS COUNTY, ILLINOIS. By HARRY MIDDLETON HYATT, M.A. (OXON.), D.D., Director of the Alma Egan Hyatt Foundation; Officer d'Académie Française; Officer de L'Order de la Couronne, Royale de Belgique. Pp. 723. New York: Alma Egan Hyatt Foundation, 1935. Price, \$6.00.

THIS colorful collection of aphorisms contains rich material for those interested in the medical superstitions and practices of an American middle-western community whose population, in 1930, numbered 62,784. Included in the 10,949 aphorisms are a large number dealing with the physical characteristics, the care and the behavior, of infants; with such erudite subjects as sex-determination and gestation; with the signs, significance, and treatment of a generous assortment of the common diseases. As in all primitive therapeutic practices, there is a striking partiality for the use of animal excreta.

The collection offers many amusing or significant items for citation. Can one doubt, for instance, the efficacy of this: "To cure choking, let the patient chase a cow until he is tired?" A familiar example of an empirical remedy found subsequently to have a somewhat rational basis is the observation: "A bee sting will cure rheumatism." And the following might well have originated within our profession during some past period of economic distress: "Unless the doctor's bill is paid promptly, the baby will not grow."

The book will be found to be a valuable and interesting source in the study of this aspect of *Americana medica*. W. J.

DEMONSTRATIONS OF PHYSICAL SIGNS IN CLINICAL SURGERY. By HAMILTON BAILEY, F.R.C.S. (ENG.), Surgeon, Royal Northern Hospital, London; Surgeon and Urologist, Essex County Council; Consulting Surgeon, Clacton Hospital, etc. Pp. 287; 341 illustrations, many in colors. Fifth edition, revised. Baltimore: William Wood & Company, 1935. Price, \$6.50.

THIS book, in its fifth edition, is not materially different from its previous editions. It records in a very orderly manner the physical signs observed in clinical surgery as well as the method of elicitation of these signs. It is intended to be an aid to students in acquiring the art of physical examination. This aim it may well accomplish if the student uses it as a guide during his first few months in the surgical wards. J. J.

THE STOMACH AND DUODENUM. By GEORGE B. EUSTERMAN, M.D., F.A.C.P., Head of Section in Division of Medicine, The Mayo Clinic; Professor of Medicine, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota, and DONALD C. BALFOUR, M.B., M.D. (TOR.), LL.D., F.A.C.S., F.R.A.C.S., Head of Section in Division of Surgery, The Mayo Clinic; Professor of Surgery, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota, and Members of the Staff, The Mayo Clinic and The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. Pp. 958; 436 illustrations. Philadelphia: W. B. Saunders Company, 1935. Price, \$10.00.

THE two major authors together with 13 of their associates in the staff of The Mayo Clinic, representing various phases of interest, have collaborated to produce what is undoubtedly the most authoritative work on diseases of the stomach and duodenum. There are discussed in detail the physiology, pathology, methods of examination, clinical pictures, treatment,

both medical and surgical, with full details of technique. The illustrations are numerous and excellent. This is a book which no practitioner, internist or surgeon should be without. The reviewer has only one suggestion: in the next edition there should be a chapter on food allergy. R. K.

ALLERGY OF THE NOSE AND PARANASAL SINUSES. A Monograph on the Subject of Allergy as Related to Otolaryngology. By FRENCH K. HANSEL, M.D., M.S., Assistant Professor of Classical Otolaryngology, Washington University School of Medicine; Fellow of the Association for the Study of Allergy, etc. Pp. 820; 58 illustrations, 4 charts and 58 tables. St. Louis: The C. V. Mosby Company, 1936. Price, \$10.00.

THE ever-widening field of allergy now touches practically every phase of clinical medicine. Internal medicine and otolaryngology, however, include the greater part of clinical allergy. Every large allergy clinic has attached to it its own otolaryngologic staff, not only because of the great number of allergic patients who require nose and throat attention, but because their problems are peculiar and different in many ways from those of non-allergic patients. There has consequently arisen what is almost a specialty within a specialty. The author has taken an active part in the development of this field and is therefore thoroughly conversant with his subject. He has produced a book which is practically encyclopedic in its scope. The material is well presented. The illustrations are on the whole satisfactory. It is a work which no otolaryngologist and no internist who majors in allergy can afford to be without. R. K.

BIOLOGICAL EFFECTS OF RADIATION. Mechanism and Measurement of Radiation Applications in Biology, Photochemical Reactions, Effects of Radiant Energy on Organisms and Organic Products. Vols. 1 and 2. Prepared under the Auspices of the Committee on Radiation, Division of Biology and Agriculture, National Research Council, Washington. Edited by BENJAMIN M. DUGGAR, Professor of Plant Physiology and Applied Botany, University of Wisconsin, with the Coöperation of Janet Howell Clark, Kenneth S. Cole, Farrington Daniels, Gioacchino Failla, Charles Packard and Henry W. Popp. Pp. 1342; illustrated. New York: McGraw-Hill Book Company, Inc., 1936. Price, \$12.00.

THIS extensive treatise is the outcome of the work of a Committee of the National Research Council, supported by grants from the Rockefeller Foundation. The topics treated fall under the general headings of the mechanism and measurement of effects of radiant energy on organisms and organic compounds. There are 43 chapters, 18 in Vol. 1, and 25 in Vol. 2, varying in length from 10 pages to 88, with an average of about 30. The contributors come from many institutions, commercial laboratories, research institutions, government bureaus and universities. The range of interest represented is large and the authorities who contributed are among the best in this country. The result is a work which represents a notable contribution to a subject of rapidly growing importance, both in practical and theoretical fields.

The contributions of the physical scientists deal with photons, electrons. Roentgen rays and radium, ionization in biologic effects of radiation, measurement of radiation, intensity of solar radiation, photochemistry. There is also a chapter on the statistical treatment of the effects of radiation. The actions upon organisms and their products are treated in chapters with the following headings: The Effect of Radiation on Proteins; Radiation and the Vitamins; The Effects of Irradiation on Venoms, Toxins, Antibodies, and Related Substances; The Effects of Radium and X-rays on

Embryonic Development; Effects of X-rays and Radium upon Regeneration; The Biological Effectiveness of X-ray Wave-lengths; The Physiological Effects of Radiation upon Organ and Body Systems; Short Electric Wave Radiation in Biology; Biological Effects of Alpha Particles; Motor Responses to Light in the Invertebrate Animals; The Action of Radiations on Living Protoplasm; Photoperiodism; Plant Growth in Continuous Illumination; The Effects of Light Intensity upon Seed Plants; Effects of Different Regions of the Visible Spectrum upon Seed Plants; Effects of the Visible Spectrum upon the Germination of Seeds and Fruits; The Effects of Visible and Ultra-violet Radiation on the Histology of Plant Tissues; Some Infra-red Effects on Green Plants; Effect of Ultra-violet Radiation upon Seed Plants; The Effects of Radiation on Fungi; The Problem of Mitogenetic Rays; Effects of X-rays upon Green Plants; The Effects of Radium Rays on Plants; The Light Factor in Photosynthesis; The Influence of Radiation on Plant Respiration and Fermentation; Growth Movements in Relation to Radiation; Chlorophyll and Chlorophyll Development in Relation to Radiation; Radiation and Anthocyanin Pigments; Effects of Radiation on Bacteria; The Effects of Radiation on Enzymes; Induced Chromosomal Aberrations in Animals; Radiation and the Study of Mutation in Animals; Induced Mutations in Plants; Induced Chromosomal Alterations; Induced Chromosomal Alterations in Maize; Biological Effects of the Quantum Theory of Radiation Absorption in Tissues.

A mere glance at this list of titles is sufficient to show the extent to which the subject of radiations has become biologic in its influence. The natural frequency of mutations may be stepped up many times, normal cells may be transformed into neoplasms, modifications of pathogenicity in bacteria may be produced, the activities of enzymes may be attenuated or destroyed, chromosomal aberrations of various kinds may be produced, and many other biologic effects are here reported. It is apparent, however, from reading the various contributions in this work that the subject of the biologic effects of radiations is in its infancy and that many of the conclusions so far reached are tentative. The amount of work already accomplished is nevertheless surprisingly large and has served to clearly indicate the great value of this new tool.

There is naturally considerable variation in the thoroughness and completeness of the various chapters of this work. In general, they are satisfactory expositions of the different phases of the subject and are supported, in most cases, by adequate outlines, bibliographies, and index entries. As a work of reference and as a guide to further investigations, "Biological Effects of Radiation," will certainly make a large contribution. Because of the rapid development of the subject, it is especially unfortunate that publication was delayed so long after the receipt of earlier manuscripts.

C. McC.

JOHANNES DE MIRFELD OF ST. BARTHOLOMEW'S, SMITHFIELD, HIS LIFE AND WORKS. By SIR PERCIVAL HORTON-SMITH HARTLEY, C.V.O., M.A., M.D., F.R.C.P., Consulting Physician to St. Bartholomew's Hospital and to the Brompton Hospital, etc., and HAROLD RICHARD ALDRIDGE, M.A., Formerly Scholar of Peterhouse, Cambridge, etc. Pp. 191. Cambridge: At the University Press. New York: The Macmillan Company, 1936. Price, \$4.50.

ST. BARTHOLOMEW'S, oldest of British hospitals, is appropriately the place with which this work, the first writing of a medical nature connected with a known British hospital, is associated. Little was known of its author, John Mirfeld, beyond that he lived and wrote in the latter half of the 14th

century, when Chaucer was writing and the Plantagenets bringing to a close their colorful dynasty. He may well have been in the hospital when Wat Tyler was brought there to die. The authors have brought to light new evidence that Mirfeld was a member of a powerful Yorkshire family and that he resided in the priory, where he wrote the two works, "Breviarium Bartolomei" and "Florarium Bartolomei." These characteristically medieval compilations of Hippocrates, Galen, Rhazes and the Arabians, the Schola Salernitana, Bernard of Gordon and others give a good picture of the state of medicine of the time of Richard II.

E. K.

MARCONITERAPIA. TRATTATO SULLE ONDE CORTE: Nella Biologia e Nelle Applicazioni Terapeutiche. By PROF. PIETRO CIGNOLINI, Capo del reparto Radiologico ed Aiuto volontario dell'Istituto di Clinica Medica Generale della R. Università di Genova. In collaboration with PROF. F. BARATTA, ING. A. ASCIONE and DOTT. C. BIANCHI. Preface by PROF. GIUSEPPE SABATINI, Direttore della Clinica Medica Generale della R. Università di Genova. Pp. 362; 152 illustrations and 12 tables. Milan: Ulrico Hoepli, 1936. Price, Lire 50.

THE book is divided into 3 parts: 1, Physical and Technical; 2, Biological; 3, Therapeutic Application. Part 1, prepared by non-medical collaborators, presents material such as one expects to find in books on physics and electricity. In the biologic section, the damage of microorganisms is attributed to thermic effects rather than to any specific effect of the rays. The nationalism that finds expression in the title is apparent in various ways throughout the text. The reader must form his own opinion as to whether the book lives up to its advertisement as the first complete organic and systematic treatise on this subject.

E. K.

DOCTOR OF THE NORTH COUNTRY. By EARL VINTON MCCOMB, M.D. With a Preface by LOGAN CLENDENING, M.D. Pp. 238. New York: Thomas Y. Crowell Company, 1936. Price, \$2.00.

BAUERNDOKTOR. By MENHOFERS FRANZEF. Pp. 184. Munchen: Verlag der ärztlichen Rundschau, 1936. Price: paper, Rm. 2.81; bound, Rm. 3.60.

THE country practitioner is rightly cherished as the backbone of our profession. He it must have been whom Stevenson picked as above the common herd, "the flower of our civilization . . . who shared but little in the defects of the period and most notably exhibited the virtues of the race." His life, too, seems to afford the best opportunity for romantic dramatization, and no better food for thought can be put in the hands of a prospective medical student than such moving stories as "Rab and his Friends," and Maclaren's "A Doctor of the Old School" (in "Beside the Bonnie Brier Bush"). Following close on their heels is McComb's "Doctor of the North Country," a doctor's account of a medical career in the lumber country of northern Michigan, an account that has the added advantage of being biographic, not fiction. The tales drip truth and hold the reader from start to finish with the skillful simplicity of the author's style. First the boy, son of a country doctor, learning to love his future profession for its hard won satisfactions, then the man's vicissitudes and "half laughs" of the day's work—epidemics, obstetrics, the problems of sex and of bill payments and finally some unexplained psychic phenomena, all the more impressive because of their simple presentation. It is good to be reminded, too, that even in these days of motors and socialized medicine, the romantic life of the "old fashioned doctor" still continues.

Less ambitious in form and scope, but none the less charming is Menhofers Franzel's "Bauerndoktor." With a more apparent appreciation of the natural surroundings of his existence, this German "farmer's doctor" understandingly pursues his chosen task in a way that we like to think of as characteristic of pre-war Germany, or at least of many parts of it. To an American reader, the episodes have the charm of novelty: What chance in this country of being driven miles through a snowstorm behind a pair of the finest horses, owned by a gypsy king, to deliver his long-overdue daughter by fitful stovelight in the hay of a gypsy wagon!

The same hard work by day and night and the same satisfaction in this same hard work is apparent in both books. Both of these doctors are optimists and both are beloved by their communities. Who should ask for more?

E. K.

THE ADRENALS. By ARTHUR GROLLMAN, PH.D., M.D., Associate Professor of Pharmacology and Experimental Therapeutics, and formerly Associate Professor of Physiology, in the Medical School of The Johns Hopkins University. Pp. 410; 17 illustrations. Baltimore: The Williams & Wilkins Company, 1936. Price, \$5.00.

THIS is a very useful monograph dealing with all aspects of the adrenals from the experimental and clinical points of view.

The author's conception of the adrenals is that structurally and functionally they consist of 3 parts: medulla, cortex proper and the inner zone of the cortex. For the last he has originated the term "androgenic tissue," because he thinks that it "has some, as yet incompletely defined function relating to the reproductive system." He believes that it is tumor formation of the cells of the androgenic zone which causes virilism, while cortical adenomas not associated with symptoms are derived from other portions of the cortex. This conception is interesting and a good working hypothesis.

In all other respects, the author expresses conventional and soundly substantiated views. If anything, he is ultraskeptical, as in regard to the emergency theory of the adrenal medulla, where he repeatedly makes emphatic statements of the "failure of investigators to demonstrate the function of the adrenal medulla." Considering the fact that he describes various conditions under which epinephrin is secreted, as for instance, after large doses of insulin, one concludes for one's self that there is valid concrete evidence that the adrenal medulla manifests a useful function in opposing various pathologic conditions, even though under normal conditions no function is determinable.

A few typographical errors were noted: the use of hyperglycemia three times (pp. 201, 202 and 203) when hypoglycemia is intended, of hypophysectomy when adrenalectomy is intended (p. 211), which might be confusing to casual readers.

The book will prove very useful in making easily available most of the significant literature on the adrenals, including the author's own important investigations.

I. Z.

COLLECTED WRITINGS. ALFRED F. HESS, 1875-1933. In Two Volumes. Pp. 1444; 127 illustrations, 124 charts and many tables. Springfield, Ill.: Charles C Thomas, 1936. Price, \$15.00.

THIS is really a correlated selection of the finest contributions of one of the most noted clinical investigators of our time.

The first volume is introduced by a splendid and sympathetic biography of Dr. Hess written by Abraham Flexner. This is no grandiloquent eulogy

but a faithful, honest appreciation of the life and work of a scholar, teacher, physician and cultured gentleman.

The variety of subjects studied and reported by Dr. Hess is amazing, especially in the light of the fact that each paper is a real contribution to medical literature. During the later years of his life, Dr. Hess' thoughts and efforts were directed mainly to the diseases of nutrition, scurvy and rickets. In these fields he made his greatest contributions. It is significant that the modern work on rickets, including its prevention and treatment will always be associated with the name of Alfred Hess rather than with those who patented similar work.

These two volumes will be greeted with appreciation and reverence by all of those who know Dr. Hess, and also by those who will care to consult the fundamental principles of certain aspects of Pediatrics so ably set forth by such a resourceful and brilliant clinical investigator.

E. T., JR.

MEDIZINISCH-CHEMISCHE BESTIMMUNGAMETHODEN. VOL. II. Eine Auswahl von Method für das klinische Untersuchungslaboratorium. By DR. KARL HINSBERG, a. o. Professor Vorsteher der chemischen Abteilung des pathologischen Instituts der Universität Berlin. Pp. 186; 48 illustrations, many tables. Berlin: Julius Springer, 1936. Price, Rm. 8.70.

THIS is the second volume of selected methods for use in the clinical laboratory, of which the first was reviewed in this Journal (190, 274, 1935). It covers inorganic materials (48 pages) carbohydrates, proteins and fats (73 pages), ferments, vitamins and hormones (17 pages) and hydrogen-ion concentration (44 pages). Preferable techniques are adequately presented, as are the results to be expected in various conditions.

E. K.

THE PATIENT AND THE WEATHER. VOL. I, PART 2. AUTONOMIC INTEGRATION. By WILLIAM F. PETERSEN, M.D., with the assistance of MARGARET E. MILLIKEN, S.M. Pp. 781, lithographed; 366 illustrations. Ann Arbor, Mich.: Edwards Brothers, Inc., 1936. Price, \$9.00.

IN this series of five or six monographs, the first to appear was Vol. III, next Vol. II, and then Part 1 of Vol. I. Failure to release them consecutively has been somewhat confusing, and the announcement that each volume is individually complete, is not fully borne out in the text, by reason of references to more detailed consideration of subjects in other volumes. Nevertheless the diligence and intelligence shown by Dr. Petersen in assembling the data for this most difficult problem, compels our admiration.

It is here contended that the organism adjusts to the meteorologic environment through the components of the autonomic system—chemical, endocrine and nervous. Interdependent rhythmic variations of action is shown in oxidation, pH, metabolism and blood pressure, in their relation to the meteorologic environment; and failure to maintain their proper balance may lead to dysfunction, disease and finally death.

Beginning with constitution, a few of the many subjects discussed are: atmospheric environment, atmosphere and the individual, moods and their psychologic implications, growth, reactions of normal pyknic and normal leptosome individuals, detailed studies of male and female subjects, reaction of children, blood changes, Wassermann and Kahn reactions. The text is elucidated by many graphs, sometimes so complete as to show twenty-one variants, wherein a comparison is made of the patient's physiologic manifestations with that of the surrounding meteorologic phenomena. An abundant, relevant bibliography is found at the end of most chapters but, so far, the monographs have lacked indices.

More inclusive environmental information is given by Hellpach in his fourth edition of "Geopsyche," so that in addition to weather conditions, he also considers the diurnal and season changes, the lunar cycle, together with the local geographic and geologic influences.

N. Y.

NEUROLOGICAL SURGERY. By LOYAL DAVIS, M.S., M.D., PH.D., D.Sc. (Hon.), Professor of Surgery and Chairman of the Division of Surgery, Northwestern University Medical School, Chicago. Pp. 429; 172 illustrations and 2 plates. Philadelphia: Lea & Febiger, 1936. Price, \$6.00.

THIS monograph, written primarily for the general practitioner to assist him in diagnosis and in the advice he may give patients requiring neurosurgical therapy, is a welcome addition to surgical literature. There are 12 chapters covering diagnosis, cranio-cerebral injuries, intracranial tumors, spinal cord tumors and injuries, injuries of the peripheral nerves, the sympathetic nervous system and epilepsy.

The volume is clearly and concisely written, and well arranged. The illustrations in black and white are excellent. The known facts are presented without the controversy which so frequently attends the development of a new field of medicine. Although the author says that the work was written for the general practitioner, it will be of considerable value to the general surgeon. There is no book now available which in so short a space covers the same ground nor are there many volumes which are so well written.

I. R.

PRINCIPLES AND PRACTICE OF RECREATIONAL THERAPY FOR THE MENTALLY ILL. By JOHN EISELE DAVIS, Senior Physical Director, Veteran's Administration Facility, Perry Point, Md.; Fellow of the American Physical Education Association. In collaboration with DR. WILLIAM RUSH DUNTON, JR., Instructor in Psychiatry, Johns Hopkins University. Pp. 206. New York: A. S. Barnes and Company, 1936. Price, \$3.00.

To have succeeded in developing a system of physical therapy for the resocialization in this group of difficult patients, is an achievement. Here are given details of the methods these authors employ to capture the attention and to arouse the interest in the psychotic and neurotic, through "voluntary and expressive activity . . . vitalized by the expansive play spirit, sustained by deep-rooted pleasurable attitudes and evoked by wholesome emotional release." This unique volume is a valuable adjunct in treatment and merits a favorable reception.

N. Y.

NEW BOOKS.

The Clinical Use of Digitalis. By DREW LUTEN, A.B., M.D., Associate Professor of Clinical Medicine in the Washington University School of Medicine and Physician to Barnes Hospital, St. Louis. Pp. 226; illustrated. Springfield, Ill.: Charles C Thomas, 1936. Price, \$3.50.

A Preface to Nervous Diseases. By STANLEY COBB, A.B., M.D., Bullard Professor of Neuropathology, Harvard Medical School; Psychiatrist in Chief, Massachusetts General Hospital. Pp. 173; 13 illustrations. Baltimore: William Wood & Co., 1936. Price, \$2.50.

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- Lane Medical Lectures: Studies in Cardiovascular Regulation.* By G. V. ANREP, M.D., D.Sc., F.R.S., Professor of Physiology, Medical Faculty, Egyptian University, Cairo, Egypt. Pp. 118; 38 illustrations. Stanford University, Calif.: Stanford University Press, 1936. Price: Paper, \$1.50; Cloth, \$2.25.
- Diseases of the Nails.* By V. PARDO-CASTELLO, M.D., Formerly Assistant Professor of Dermatology and Syphilology, University of Havana; Member of the American Dermatological Association, etc. With a Foreword by HOWARD FOX, M.D., Professor of Dermatology and Syphilology, New York University, University and Bellevue Hospital Medical College. Pp. 177; 94 illustrations. Springfield, Ill.: Charles C Thomas, 1936. Price, \$3.50.
- Classification of Yeasts and Yeast-like Fungi.* By C. VIRGINIA FISHER, Ph.D., on Fleischmann Grant for Mycological Investigation, and LLOYD ARNOLD, M.D., Professor of Bacteriology and Public Health. Pp. 92; 10 plates. Urbana, Ill.: University of Illinois Press, 1936. Price, \$1.00.
- Pathology of the Nervous System. A Students Introduction.* By J. HENRY BIGGART, M.D. (BELFAST), Pathologist to the Scottish Asylums' Board; Neuropathologist to the Royal Infirmary, Edinburgh; Lecturer in Neuropathology, Edinburgh University, etc. Foreword by PROFESSOR A. MURRAY DRENNEN, M.D., F.R.C.P. Pp. 335; 204 illustrations. Baltimore: William Wood & Co., 1936. Price, \$5.25.
- Digestion and Health.* By WALTER B. CANNON, George Higginson Professor of Physiology, Harvard Medical School. Pp. 160; 14 illustrations. New York: W. W. Norton & Co., Inc., 1936. Price, \$2.00.
- Die Nebennierenrinde.* Beiträge zur Experimentellen und Klinischen Pathologie. By DR. MED. SIGISMUND THADDEA, Assistent der II. Med. Universitätsklinik der Charité, Berlin. Pp. 199; 78 illustrations, 36 tables. Leipzig: Georg Thieme, 1936. Price: Paper, M. 11; Bound, M. 13.
- The Art of Treatment.* By WILLIAM R. HOUSTON, A.M., M.D., F.A.C.P., Formerly Professor of Clinical Medicine, University of Georgia; Formerly Visiting Professor of Medicine, Yale-in-China. Pp. 744. New York: The Macmillan Company, 1936. Price, \$5.00.
- Abstracts. Proceedings of the New York Pathological Society,* held November 22 and December 27, 1934; January 24, February 28, March 28, April 25 and May 23, 1935. Reprinted from the Archives of Pathology. Pp. 41. (No price given.)
- Principles of Biochemistry.* By ALBERT P. MATHEWS, Andrew Carnegie Professor of Biochemistry, University of Cincinnati, Cincinnati, Ohio. Pp. 512; 3 illustrations. Baltimore: William Wood & Co., 1936. Price, \$4.50.
- The Riddle of Woman. A Study in the Social Psychology of Sex.* By DR. JOSEPH TENENBAUM. Pp. 477. New York: Lee Furman, Inc., 1936. Price, \$3.50.
- Urological Roentgenology.* By MILEY B. WESSON, M.D., Ex-President American Urological Association, and HOWARD E. RUGGLES, M.D., Roentgenologist to University of California Hospital, St. Luke's Hospital, and Clinical Professor of Roentgenology, University of California Medical School. Pp. 269; 227 illustrations. Philadelphia: Lea & Febiger, 1936. Price, \$5.00.
- Favourite Prescriptions.* (The Practitioner Handbooks.) Edited by SIR HUMPHRY ROLLESTON, Bt., G.C.V.O., K.C.B., M.D., F.R.C.P., and ALAN A. MONCRIEFF, M.D., F.R.C.P. Pp. 227. London: Eyre & Spottiswoode, Ltd., 1936. Price, 10/6.

A Dissertation on the Sensible and Irritable Parts of Animals. By ALBRECHT VON HALLER [London, J. Nourse, 1735]. Introduction by OWSEI TEMKIN. Pp. 49; 1 illustration. Baltimore: The Johns Hopkins Press, 1936. Price, \$1.00.

Il Mondo senza Donne (El Mundo sin Mujeres). By LETRUSCO. Pp. 180. Guayaquil: Aliprandi & Martini, n.d. (No price given.)

"Hippokrates." Wochenschrift für Biologische Medizin in Theorie und Praxis, Organ für die Einheitsbestrebungen in der Medizin. Vol. 32, No. 7, September 24, 1936 (Special Robert Bosch Number). Pp. 47; 1 illustration. Stuttgart: Hippokrates-Verlag, G.M.B.H., 1936. Price, Single copy, Rm. .50; Per Year, Rm. 18.00.

Homoöpathie-Allopathie. Unfertige und Fertige. Herzklappenfehler, Eine Klinische Beweisführung. By DR. MED. KARL FAHRENKAMP, Stuttgart. Pp. 181. Stuttgart: Hippokrates-Verlag, G.M.B.H., 1936. Price, Paper, Rm. 7.25; Bound, Rm. 8.25.

The title of the book is somewhat misleading. Instead of a discussion of the problem: homœopathy-allopathy, the reader finds a thorough treatise of the developing and fully developed mitral stenosis and its treatment from the allopathic point of view. W. E.

Nutritive and Therapeutic Values of the Banana. A Digest of Scientific Literature. Pp. 141; 1 illustration. Boston: Research Department, United Fruit Company, 1936. (No price given.)

This Digest abstracts 292 articles, mostly favorable, on the nutritive and therapeutic uses of the banana. The articles arranged alphabetically by author are all indexed.

Krebs Neue Streng Sachliche Krebslehre. By MED. DR. JOSEF LARTSCHNEIDER, Linz a. d. Donau. Pp. 143; 15 illustrations. Wien: Franz Deuticke, 1936. Price, M. 4.00.

Among the strange theories that are now and then put forth about the origin of cancer, this stands out as a curiosity.

Differentialdiagnose in der Inneren Medizin. Lieferung 2. 1.-6. Tausend. By PROF. DR. MED. O. NÄGELI, Direktor der Medizinischen Universitätsklinik, Zürich. Pp. 414; 97 illustrations. Leipzig: Georg Thieme, 1936. Price, Rm. 9.60.

Psychiatry for Practitioners. [Reprinted from Oxford Loose-Leaf Medicine.] By various authors. Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (HON.), Hersey Professor of the Theory and Practice of Physics, Harvard University; Physician-in-Chief to the Peter Bent Brigham Hospital, Boston. Pp. 646. New York: Oxford University Press, 1936. Price, \$6.50.

Principles and Foibles of Cancer Research. In regard to Etiology and Nature. By WILLIAM RIENHOFF, SR., M.D., F.A.C.S. Pp. 200. Privately Printed by Waverly Press, Inc., Baltimore. (Price not given.)

Treatment in Psychiatry. By OSKAR DIETHELM, M.D., Professor of Psychiatry, Cornell University Medical College, New York; Psychiatrist-in-Chief, The New York Hospital (Payne Whitney Psychiatric Clinic), etc. Pp. 476. New York: The Macmillan Company, 1936. Price, \$4.00.

British Masters of Medicine. Edited by SIR D'ARCY POWER, K.B.E., F.R.C.S., F.S.A., Consulting Surgeon and Archivist to St. Bartholomew's Hospital; Honorary Librarian, Royal College of Surgeons of England. Pp. 242; illustrated. Baltimore: William Wood & Co., 1936. Price, \$3.00.

The Gift of Columbus. By CHARLES C. DENNIE, M.D., Kansas City, Mo. Pp. 195. Kansas City, Mo.: Brown-White Company, 1936. Price, \$2.00.

NEW EDITIONS.

Anatomy of the Human Body. By HENRY GRAY, F.R.S., Fellow of the Royal College of Surgeons; Lecturer on Anatomy at St. George's Hospital Medical School, London. Pp. 1381; 1216 illustrations. Twenty-third Edition, thoroughly Revised and Re-edited by WARREN H. LEWIS, B.S., M.D., Professor of Physiological Anatomy, Johns Hopkins University, Baltimore, Md.; Research Associate, Carnegie Institution of Washington. Philadelphia: Lea & Febiger, 1936. Price, \$10.00.

A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology. By TORALD SOLLMAN, M.D., Professor of Pharmacology and Materia Medica in the School of Medicine of Western Reserve University, Cleveland. Pp. 1190; 22 illustrations. Fifth Edition, entirely reset. Philadelphia: W. B. Saunders Company, 1936. Price, \$7.50.

The general plan of previous editions of this valuable textbook has been followed in the present edition. Some 29 topics have been revised and others modified, so that the text was entirely reset.

Materia Medica and Therapeutics. A Text-Book for Nurses. By LINETTE A. PARKER, B.Sc. (Columbia University), R. N., Bachelor's Diploma in Education, Teachers College; Formerly Instructor in Nursing and Health, Teachers College, Columbia University. Pp. 377; 32 illustrations and 3 plates in color. Sixth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, \$2.50.

"The aim of this book is to present the study of drugs from a scientific basis in such a way as to appeal to the nurse's interest. . . . The new Pharmacopœia called for the omission of some formerly well known drugs, such as strophanthus and the resinous cathartics. . . . Many of the proprietary remedies which have not proven of value are omitted" and some 40 or 50 new preparations added.

Fundamentals of Human Physiology. By the Late J. J. R. MACLEOD, M.B., D.Sc., F.R.S., Late Regius Professor of Physiology in the University of Aberdeen, Scotland; Formerly Professor of Physiology in the University of Toronto, etc., and R. J. SEYMOUR, M.S., M.D., Professor of Physiology, Ohio State University, Columbus. Pp. 424; 108 illustrations. Fourth Edition. St. Louis: The C. V. Mosby Company, 1936. Price, \$2.50.

This revision retains the stellar qualities upon which the wide usefulness of its predecessors has been based. The chapters on the vitamins and the endocrine glands show the most modification since the 1924 edition. Metabolism and immunity have been presented in more simplified form. Many additional diagrams and figures will prove advantageous to the elementary student. O. S.

Starling's Principles of Human Physiology. Edited and Revised by C. LOVETT EVANS, D.Sc., F.R.C.P., F.R.S., LL.D. B'ham, Jodrell Professor of Physiology in University College, London. The Chapters on the Central Nervous System and Sense Organs revised by H. HARTRIDGE, M.A., M.D., Sc.D., F.R.S., Professor of Physiology at St. Bartholomew's Medical College. Pp. 1096; 554 illustrations (6 in color). Seventh Edition. Philadelphia: Lea & Febiger, 1936. Price, \$8.75.

A Text-Book of Physiology, for Medical Students and Physicians. By WILLIAM H. HOWELL, PH.D., M.D., Sc.D., LL.D., Emeritus Professor of Physiology in The Johns Hopkins University, Baltimore. Pp. 1150; 308 illustrations. Thirteenth Edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1936. Price, \$7.00.

A Text-Book of Pharmacology and Therapeutics or the Action of Drugs in Health and Disease. By ARTHUR R. CUSHNY, M.A., M.D., LL.D., F.R.S., Late Professor of Materia Medica and Pharmacology in the University of Edinburgh. Pp. 808; 70 illustrations. Eleventh Edition, thoroughly revised by C. W. EDMUNDS, A.B., M.D., Professor of Materia Medica and Therapeutics and Director of the Pharmacological Laboratories in the University of Michigan, Ann Arbor, and J. A. GUNN, M.A., M.D., D.Sc., F.R.C.P., Professor of Pharmacology and Director of the Nuffield Institute for Medical Research, University of Oxford, Oxford, England. Philadelphia: Lea & Febiger, 1936. Price, \$6.50.

Principles of Chemistry. An Introductory Textbook of Inorganic, Organic and Physiological Chemistry for Nurses and Students of Home Economics and Applied Chemistry. With Laboratory Experiments. By JOSEPH H. ROE, Professor of Biochemistry, School of Medicine, George Washington University; Formerly Instructor in Chemistry, Central School of Nursing, Washington, D. C. Pp. 475; 39 illustrations, and 2 colored plates. Fourth Edition. St. Louis: The C. V. Mosby Company, 1936. Price, \$2.75.

This book, as the title implies, purports to cover the entire field of chemistry required in the training of nurses and students of home economics. The treatment accorded to each particular topic is necessarily very brief but the author succeeds well in his attempt to provide a comprehensive chemistry textbook for such students. In this, the fourth edition, a number of revisions have been made, particularly in order to bring the book more nearly up to date in the fields of vitamins and hormones. Laboratory experiments are also included. J. A.

Roentgen Interpretation. A Manual for Students and Practitioners. By GEORGE W. HOLMES, M.D., Roentgenologist to the Massachusetts General Hospital and Clinical Professor of Roentgenology, Harvard Medical School, and HOWARD E. RUGGLES, M.D., Roentgenologist to the University of California Hospital and Clinical Professor of Roentgenology, University of California Medical School. Pp. 356; 243 illustrations. Fifth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, \$5.00.

Modern Urology. In Original Contributions by American Authors. Vol. 1. General Considerations—Diseases of Penis and Urethra—Diseases of Scrotum and Testicle—Diseases of Prostate and Seminal Vesicles. Pp. 951; 546 illustrations and 12 plates (some in color). Vol. II. Diseases of the Bladder—Diseases of the Ureter—Diseases of the Kidney—Radiation Therapy of Tumors of the Genito-urinary Tract. Pp. 862; 374 illustrations and 9 colored plates. Edited by HUGH CABOT, M.D., LL.D., C.M.G., F.A.C.S., Professor of Surgery, The Mayo Foundation, Graduate School of the University of Minnesota, and Consulting Surgeon to The Mayo Clinic, Rochester, Minn.; Formerly Dean and Professor of Surgery in the Medical School of the University of Michigan, Ann Arbor. Philadelphia: Lea & Febiger, 1936. Third Edition, thoroughly revised. Price, \$20.00.

A Textbook of Surgery. By JOHN HOMANS, M.D., Clinical Professor of Surgery. Compiled from Lectures and Other Writings of 23 Members of the Surgical Department of The Harvard Medical School. With a Special Bibliographical Index and Illustrations by Willard C. Shepard. Pp. 1267; 530 illustrations. Fourth Edition. Springfield, Ill.: Charles C Thomas, 1936. Price, \$8.00.

Bailey's Text-book of Histology (Elwyn and Strong). By PHILIP E. SMITH, Professor of Anatomy, Editor; RUSSELL L. CARPENTER, Ph.D., WILFRED M. COPENHAVER, Ph.D., CHARLES M. GOSS, M.D., AURA E. SEVERINGHAUS, Ph.D., all Assistant Professors of Anatomy, College of Physicians and Surgeons, Columbia University. Pp. 773; 506 illustrations, some in colors. Ninth Edition, Revised and Rewritten. Baltimore: William Wood & Co., 1936. Price, \$6.00.

Recent Advances in Endocrinology. By A. T. CAMERON, M.A., D.Sc. (Edin.), F.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital. Pp. 458; 65 illustrations, including 3 plates. Third edition. Philadelphia: P. Blakiston's Son & Co. Inc., 1936. Price, \$5.00.

A Practical Medical Dictionary. By THOMAS LATHROP STEDMAN, A.M., M.D. Pp. 1282; illustrated. Thirteenth Edition, Revised, with the New British Anatomical Nomenclature (9 pages). Baltimore: William Wood & Co., 1936. Price, \$7.50 with thumb index; \$7.00 without.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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HEART DISEASE IN PREGNANCY.

THE chaotic state of our knowledge concerning the relationship of heart disease to pregnancy has gradually given way, particularly in the past 15 years, to a more orderly organization of the problem at hand. The reports of the past 5 years reflect not only the organization of the problem, but also the application of the newer knowledge of cardiology. Should the cardiac patient become pregnant? What may we expect if she does become pregnant? Should the pregnancy go to term? Is intervention advisable? What method of delivery is the procedure of choice? Which anesthetic is to be preferred? Should sterilization be done? These are among the questions having no final answers as yet, but for which definite helpful rules have been formulated.

The Effect of Pregnancy Upon the Normal Heart.—Pregnancy virtually converts woman into a new physiologic organism. Many anatomic as well as physiologic changes occur. "From the very moment the ovum is implanted in the uterus, it keeps on exacting more and more from the maternal organism; and during the 9 months of normal pregnancy, there is a steady increase of the demands from practically every organ of the mother."²³ Metabolism is distinctly affected. Both anabolic and catabolic processes are accelerated. New endocrine equilibria develop. The fetus enlarges and with it the uterus. New demands are made upon the circulation and consequently upon the heart.

Little is known of the effects of pregnancy upon the heart. "Only when we have a clear understanding of how the normal heart acts in normal pregnancy are we able to account for the heart action in various diseases of pregnancy and, especially, to appraise the effect of pregnancy on the injured heart."²³ While these reactions have been the object of many investigations, those of Gammeltoft²³ and of Stander and his group^{53,54} are most important.

Gammeltoft studied 239 cases with regular examinations throughout the entire period of pregnancy. All were primiparæ or secundiparæ of normal physique. Examinations were made every 2 to 3 weeks from the second or third month on. In the majority of cases circulatory

symptoms did not develop and aside from soft systolic murmurs, premature beats and accentuation of the pulmonic second sound, usual clinical methods demonstrated no changes. Most interesting, however, was the fact that 39 of the 239 healthy individuals developed definite circulatory symptoms in the last half of pregnancy, sufficient in the last 2 months to suggest heart disease. Of the 39, 24 developed dyspnea; 19 had albumin in the urine; 34 had edema. Physical examination disclosed evidence of cardiac enlargement, tachycardia, murmurs and accentuation of the second pulmonic sound. Gammeltoft describes these murmurs as functional in type, rarely apical and both systolic and diastolic in time. The usual procedures affecting cardiac function (work, rest in bed, digitalis) had no effect. Blood pressures were normal. Deliveries were uneventful and examinations in the puerperium disclosed the disappearance of practically all symptoms and signs. "I find it of the greatest importance that the obstetrician as well as the general practitioner realize that such functional—gestatory—heart disturbances do occur in pregnancy, that they are relatively frequent, and that they are of no consequence whatever during parturition." Systemic examination throughout the entire period of gestation is stressed as important in differentiating these cases from organic heart disease. Gammeltoft further states that, if these patients are first seen late in pregnancy, misdiagnosis may result, and that there is no doubt that such cases are frequently included in statistics on organic heart disease.

Two of the signs regarded as pathognomonic of heart disease appear to lose their full diagnostic significance in pregnancy. These are, 1, the diastolic murmur, and 2, cardiac enlargement. The occurrence of diastolic murmurs in pregnancy without organic valvular disease has been mentioned above. They are, however, basal and in cases seen by the writer, blowing in character, and disappear postpartum. Confusion with the murmur of mitral stenosis, therefore, does not occur.

The increased cardiac dulness to percussion and the increased diameters to Roentgen ray measurement are ascribed by most observers to cardiac displacement resulting from increased height of the diaphragm following uterine enlargement. Transverse position of the heart, it is well known, can explain these findings. Enlargement of the breasts may make examination more difficult so that enlargement is erroneously diagnosed. Another school, however, believes that actual hypertrophy or dilatation exists.^{19,23} The findings are controversial. Indeed the minute volume output of the heart is increased.^{23,53,54} Stander and Cadden,⁵³ using the more accurate acetylene method, have shown that normal pregnancy is accompanied by a progressive increase in cardiac output as term is approached. This increase amounts to over 50% in the latter half of pregnancy and "as normal pregnancy is not associated with an appreciable fall in blood pressure it is apparent that normal gestation is accompanied by a marked increase in cardiac work." Stander is unable to state whether this additional cardiac work is effected by actual hypertrophy of the heart, or by calling into function any reserve force of the heart. Reid^{43a} doubts the necessity for the assumption that increased cardiac output means a marked increase in cardiac work.

The incidence of cardiac failure increases, in the presence of heart disease, as pregnancy progresses. The fact that the cardiac output

increases appreciably from the fourth month on leaves no doubt that the damaged heart is severely taxed as pregnancy progresses. Consequently, failure early in pregnancy portends a serious outcome. Even though in experimental animals²⁹ no change in heart size with pregnancy was demonstrated, and although similar studies in women³² have been negative, the increase in cardiac work may cause hypertrophy which is not grossly apparent.

Change in the position of the heart can explain not only the apparent enlargement but may explain very simply many of the electrocardiographic changes accompanying pregnancy. Feldman and Hill,²¹ among others, describe the left axis deviation which occurred in 24 of 36 patients without heart disease. In 17 of the 24, T_a was negative. These findings occur typically in transverse hearts. Correlation with the height of the uterus showed that 80.88% had changes in the electrocardiogram at the greatest height of the uterus. The results of Carr and Palmer⁷ were similar in many respects. The development of a large Q wave in Lead III with disappearance following delivery has been described^{8,20} and these changes have been shown to correlate closely with a transverse position of the heart.

The strict use of measurement of components of the $Q R S$ complex to determine hypertrophy of one chamber or the other, as Gammeltoft's co-workers have done, cannot be accepted because of our lack of knowledge of the significance of these components, and because of the fact that cardiac displacement may result from movement in more than one plane, interfering with the calculations interpreted as indicating hypertrophy. The occurrence of these changes in correlation with uterine height points to displacement as a cause of the cardiac dullness and measurement changes. A high diaphragm, as well, can explain the reduced vital capacity and account for the dyspnea and the accentuated P_2 .

The Diagnosis of Heart Disease in Pregnancy. The incidence of organic heart disease in pregnancy varies, among many factors, with the soundness of the criteria used in diagnosis, geographical distribution and the type of patient attracted to the reporting clinic. For example, when the clinic at Boston Lying-in Hospital was started, the incidence of heart disease was 0.65%. This percentage subsequently rose to 1.5%, due not only to increasingly careful examination, Carr and Hamilton⁶ believe, but also to the fact that the cardiac clinic attracted patients with heart disease who would not have gone to the hospital if they had had no heart disease. In general, the incidence of heart disease in pregnancy is about 1%. Reis and Frankenthal¹¹ found 102 of 7670 patients with heart disease (1.33%). Herrmann and King²¹ report 24 (1.38%) in 1746 white women. Schulze⁴⁷ reports 118 (1.1%) in 10,562 patients; Donovan, in England,¹⁸ 52 (0.255%) in 20,306 deliveries; Lamb,^{33a} 50 (2.7%) in 2193 patients; Fitzgerald,²² 126 (0.66%) in 19,000 cases; Stander,⁵² 81 (4.15%) in 1951 cases; Hanley and Anderson,²⁷ 65 (0.44%) in 14,700 cases, and Daichman and Kornfeld,¹³ 205 (0.93%) in 22,100 cases. In this entire group 823 patients with organic heart disease were found in 100,228 obstetrical cases, an incidence of 0.82%.

When apparent enlargement of the heart with dyspnea and various murmurs is accompanied by edema of the ankles, determination of

exact cardiac status is most difficult. It is here that the guides and principles outlined by Reid^{43a} are advantageously followed in determining the presence or absence of organic heart disease. Below the age of 40—and most pregnancies occur, of course, below that age—Reid considers a diagnosis of heart disease rarely justifiable in the absence of one or more of the chief reliable signs. A similar group of findings has been enumerated by Herrmann.³⁰

Hamilton and Kellogg^{26a} found that 7.5% of all women entering the pregnancy clinic had something in the history or physical examination to require a decision on the heart. Breed and White state that 50% of pregnant women presenting cardiac signs and symptoms do not have organic heart disease.⁵ The difficulties described by Gammeltoft have already been mentioned. The extreme importance of eliciting pathognomonic evidences of organic heart disease, therefore, becomes apparent. Essentially these are:

1, Definite cardiac enlargement. That this finding must be used with caution has already been discussed.

2, Serious mechanisimal disturbances, such as true pulsus alternans, heart block not due to digitalis, auricular flutter, and auricular fibrillation.

3, Definite thrills which are unmistakably cardiac. A slight vibration is insufficient.

4, An unmistakable pericardial friction rub.

5; Diastolic murmurs. Certain exceptions in pregnancy have already been mentioned.

6, Expansile pulsation of the liver.

7, Significant engorgement of the neck veins in the sitting position. While this finding may be due to the pressure of tumors and abnormal position of the diaphragm (again pregnancy may interfere), it is particularly significant if associated with enlargement of the liver and particularly an expansile pulsation of the liver.

8, Persistent arterial hypertension or widespread arteriosclerosis of long duration.

9, Typical classical angina pectoris. This finding is based on history alone and must be evaluated in that light.

While 1, 5 and 7 must be carefully evaluated in pregnancy, the remaining findings obviously mean heart disease by their very presence. In their absence, heart disease is seldom present in the child-bearing age except possibly as (a) acute rheumatic endocarditis and myocarditis, and (b) bacterial endocarditis. Even in the absence of definite signs a past history of any clear cut picture of the rheumatic syndrome, such as a typical polyarthritis or chorea, should raise the clinical suspicion of the disease to a high level.

The Etiologic Diagnosis.—The etiologic types of heart disease occurring in pregnancy are, of course, any types which may affect woman in the child-bearing age. Since rheumatic heart disease is most frequent in this group, it receives greatest consideration in any discussion of heart disease in the gravid woman. Approximately 85 to 95% of all organic heart disease in pregnancy is rheumatic.^{6,13,22,33a,38,44,47} The remaining 5 to 15% represents the usual other causes which may also be seen in this period, such as septic heart disease (bacterial endocarditis), syphilitic, thyrotoxic, hypertensive, arteriosclerotic and congenital types.

Organic heart disease, dependent upon pregnancy alone as an etiologic agent, is not recognized.

Anatomic Diagnosis.—With rheumatic heart disease accountable for 90 % of serious cardiac disturbances, the chief anatomic lesions will be, naturally, those of rheumatic heart disease. Valvular defects are, therefore, most common, particularly in the mitral valve. The most important of these is mitral stenosis. Daniels¹⁵ has compiled the data on the incidence of valvular defects as given by Kellogg, Pardee, White, McIlroy and Daly, representing a wide geographical distribution. In 590 cases, 62.5 % had mitral stenosis; 246 patients had mitral stenosis alone, 138 mitral insufficiency, 78 both lesions, 9 mitral insufficiency and aortic insufficiency, 38 double mitral lesions with aortic insufficiency, 17 aortic insufficiency alone, 7 mitral stenosis and double aortic lesions. In this series, as well, 15 cases of congenital heart disease were found, representing 2.5 % of the total number of cases. Carr and Hamilton⁶ found a similar incidence, 12 (2.4 %) in 500 consecutive cases. Of these, 5 had interventricular septal defects, 2 patent ductus arteriosus, 1 coarctation of the aorta and 4 the anomaly not identified. Any defect compatible with the child bearing age is possible. The same observers note that those without disability and with a congenital lesion which does not communicate between the right and left sides of the heart or pulmonary artery and aorta have no difficulty. Others⁵ find that those attaining the child-bearing age without incapacity usually pass through pregnancy and labor without difficulty. Shapiro and Simons⁵⁰ report successful termination of a case with the tetralogy of Fallot, indicating that high grade cyanosis is not an absolute contraindication to pregnancy. However, if a chance for shunting blood from the right to the left side of the heart exists, as in interventricular septal defect, sudden unexpected symptoms may follow the second stage of labor.⁶ Rapid respirations and heart rate may develop and death may result without congestive heart failure. Such symptoms are ascribed to the sudden release in peripheral pressure especially after Cesarean section and version. The type of congenital lesion may, therefore, influence the type of delivery and a knowledge of the presence of lesions permitting right-left shunts may lead one to anticipate and prevent serious complications. Syphilitic heart disease (aortic regurgitation, aortitis, aneurysm) is not common. In aortic regurgitation due to syphilis, the prognosis is poor and the maternal risk is great.

Carr and Hamilton found that in rheumatic heart disease, activity of the process, the biggest single factor in prognosis, had almost entirely ceased. In 472 cases averaging 1 year under observation, 472 years of rheumatic heart disease in adult women, only 3 showed evidence of activity.

In the non-valvular group, hypertrophy and dilatation accompanying hypertension and hyperthyroid states are seen. Coronary disease and its resultant changes are rare. Coronary occlusion has been reported.⁴⁴ Adhesive pericarditis is rare. It is in the non-valvular group that diagnosis becomes most difficult, especially since both the etiology and the anatomical defects may be overlooked. Care must be used in all methods of examination. In the non-valvular group, cardiac enlargement is a most important sign and one which may be confused with the normal changes of pregnancy.

Another rare, but important, anatomic type of cardiac disease in pregnancy is subacute bacterial endocarditis. Although only 8 cases have been reported as such in the American literature,³⁴ its incidence is more common as evidenced by cases in general reports.^{6,47} The disease is invariably fatal, and pregnancy does not appear to aggravate it. Conversely, the disease does not seem to affect the course of pregnancy, labor, or the puerperium.⁴⁰ There appears to be no advantage in premature delivery or Cesarean section, except to save the baby if the mother is threatened with death. There has been only one reported fetal death, and this in a premature baby. In the remaining reported cases the babies have all done well.

The Physiologic Diagnosis.—There are no mechanisimal disturbances peculiar to pregnancy. Sinus tachycardia, simple rapid pulse, is a common finding in the absence of heart disease. The same may be said for extrasystoles. Extrasystole is the most common arrhythmia both in and outside of the gravid state.

Heart Block.—Until February, 1936, there had been reported 13 cases^{3,25} of complete arterioventricular heart block in pregnancy. The most common cause of heart block, arteriosclerotic heart disease, is usually not present in the age group under discussion. Most common causes in this group are rheumatic fever, diphtheria, congenital lesions, and perhaps over-digitalization. Symptoms may be entirely lacking, or with transition from partial to complete block, dizziness, convulsions, and coma indicative of a Stokes-Adams seizure may occur. Greenhill cites Freund's case in which miscarriage occurred at the eighth month; 1½ hours later the patient died in a Stokes-Adams attack. One of McIlroy and Rendel's 2 cases³⁸ developed similar attacks postpartum. Herskovic's case, also cited by Greenhill, was similar. Symptoms are prone to develop in pregnancy, particularly postpartum. Herrmann and King's case,³¹ however, had 6 successful deliveries without any complications. Since heart block is usually a manifestation of widespread myocardial damage, it is considered a serious sign of heart disease. If caused by a lesion which is not extensive, the cardiac reserve may be little affected and patients may live 20 to 30 years without symptoms. In most reported cases, pregnancy and labor have been uneventful.^{3,25,31,56} With good compensation and in the absence of symptoms, interference in labor is contraindicated except for shortening of the second stage with low forceps. Local anesthesia is the procedure of choice.^{3,25,31} With decompensation, Greenhill advises low cervical Cesarean section with local anesthesia.

Heart block of the bundle branch type has been recognized in pregnancy.³¹ In 2 cases reported, 1 patient died in labor, the other lived following Cesarean section.

Paroxysmal tachycardia is a more common mechanisimal disturbance closely related to ectopic beats. It is estimated⁶ that close to 1% of all pregnant women have attacks. It occurs most often in those with no evidence of organic disease and is usually of no grave significance. Carr and Hamilton include 2 such patients in the group of serious heart disease because of the length and severity of the attacks. Occasionally attacks are so long and severe that death may ensue. The writer observed such a case carried through to autopsy at which no organic heart disease was evident. Such an outcome is, however, most unusual

and in pregnancy the outcome has been uniformly good. ^{2a,8b,16,39} One of these cases was interesting in that attacks ceased during the period of gestation.

As an accompaniment of organic heart disease, Carr and Hamilton observed this disturbance 7 times in 500 cases. In 1 patient with mitral stenosis an attack was followed by congestive heart failure, premature labor and death. Cesarean section is to be considered³⁹ in those patients with a serious circulatory response to the attacks, unless they are readily controlled.

Auricular fibrillation, because of its frequency and serious prognostic significance, is the most important disturbance of cardiac mechanism in pregnancy. In Carr and Hamilton's series there were only 14 instances in 500 cases. Six of the 14 occurred among 32 fatal cases. Of the fatal cases 18% had auricular fibrillation, while the incidence was only 2.8% in the entire series; 43% of those with fibrillation died. Robinson⁴⁵ records a mortality of 72% in 18 cases. These authors also remark that the incidence of auricular fibrillation in their series is remarkably low compared to the usual incidence in rheumatic heart disease outside of pregnancy, most probably due, in part at least, to age of the patients. The average age of those with auricular fibrillation was 4 years higher than that for the entire group of 500.

Pardee^{42b} recognizes auricular fibrillation as a complication which affects the plan of treatment and prognosis based otherwise solely on functional capacity. These exceptions will be noted in the functional classification given below.

Cardiac insufficiency is best considered in the diagnosis as to functional capacity.

Diagnosis as to Functional Capacity.—Functional capacity, prognostication and treatment are so closely interrelated that a discussion[†] of one naturally involves the other.

Knowing that heart disease is present, the physician has before him the most difficult problem in all medicine—prognosis. Upon it one decides the advisability of the patient's becoming pregnant, the expected course of the case, the problems of intervention and delivery, anesthesia and sterilization. Some¹² believe it is impossible to prognose the outcome of pregnancy in a cardiopath.

Before the World War, prognosis and its problems were based almost entirely upon anatomical defect. Shortly after the war, however, Mackenzie pointed out the fallacy of predictions upon the anatomical state of the heart alone. He called attention to the importance of the functional capacity of the heart as an estimation of its ability to carry through pregnancy. In 1922, Pardee reëmphasized this view, particularly from the point of view of the patient's past activities and his ability to react to certain function tests. The application of the estimation of the functional capacity of the heart as advocated by the Association for the Prevention and Relief of Heart Disease and later approved by the American Heart Association¹¹ has led to its wide-spread use and confirmation. One must remember, however, that there are certain anatomical defects and mechanisimal disturbances which violate this rule. The more important of these have already been discussed.

The classification of patients as to functional capacity as advocated

by the Criteria Committee of the Heart Committee of the New York Tuberculosis and Health Association¹¹ is as follows:

Class 1. Patients with organic heart disease able to carry on ordinary physical activity without discomfort. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or chest pain. Patients in this class do not show physical signs of cardiac insufficiency and rarely signs of active heart infection.

Class 2. Patients with organic heart disease unable to carry on ordinary physical activity without discomfort.

(a) Activity slightly limited. Ordinary physical activity causes undue fatigue, palpitation, dyspnea or chest pain. Patients in this class rarely show physical signs of cardiac insufficiency or signs of active heart infection.

(b) Activity greatly limited. Less than ordinary physical activity causes fatigue, palpitation, dyspnea or chest pain. Patients in this class usually show one or more physical signs of cardiac insufficiency or the anginal syndrome or signs of active heart infection.

Class 3. Patients with organic heart disease and with symptoms or signs of cardiac insufficiency at rest, unable to carry on any physical activity without discomfort. There is fatigue, palpitation, dyspnea or chest pain at rest. Patients in this class show marked physical signs of cardiac insufficiency or the anginal syndrome, or signs of active heart infection.

In the application of these rules to the pregnant woman one must realize that certain symptoms used in classification may arise in the normal pregnant woman. "One must compare the cardiac patient with a woman of similar physical habitus, the same stage of pregnancy and a similar degree of uterine enlargement."^{42b} Although Pardee^{42a} has advocated the use of an efficiency test, the swinging of dumb-bells, in this estimation, it is generally believed that the patient's reaction to her daily activities is as adequate a test as we have at present. It is to be remembered further that the cardiac state in pregnancy is not static, that with progress of the pregnancy, or heart disease, and changes in environmental factors, a patient may need reclassification from time to time. Nor can individualization be forgotten. Each patient is a problem unto herself, requiring her own application of general principles and rules.

In general, one may say^{42a} that patients in Class 1 will give no trouble; that those in Class 2-a most probably will not; but that those in Class 2-b may run into difficulties; while those in Class 3 present a high mortality and difficulties in management. Such conclusions are borne out by many reports not only in this country but in Europe as well. Daniels¹⁵ has collected 1364 cases from the reports of Pardee (1929), Hamilton and Kellogg (1928), Breed and White (1923), Corwin and Herrick (1927) McIlroy and Rendel (1931), Daly (1924), McClure (1932) and Gilchrist (1931). In 554 cases falling into Classes 1 and 2-a there were no deaths. Seven (6%) of 120 women in Class 2-b and 25 (9%) of 279 in Class 3 died. In 8 widely scattered clinics reporting 1364 cases, the value of the method is clearly demonstrated. Others^{13,17,27,36,37,47} have reached similar conclusions.

Objections have been raised to the use of the classification as to functional capacity. Schuman⁴⁸ states that a more simple division into mild and severe cases would be less difficult and more satisfactory. He believes that the mild cardiac can be treated as any other obstetric

patient, except for limitation of exercise and shortening of the second stage of labor. The severe cardiacs, he states, must be treated individually. Parity, the period of gestation when first seen, her ability to obey instructions, religion and desire for children are among the factors which must be taken into consideration. Bramwell^{4b} divides his cases into three groups: 1, the most serious, such as those with auricular fibrillation or congestive failure in the past; 2, those with failure during the later months of pregnancy; and 3, trivial cases. Hamilton and Kellogg^{26b} classify their patients chiefly on anatomic defects. In Class 1, they place patients with severely injured or disordered hearts, chiefly because of enlargement, a diastolic murmur, or both. These are cases of definite heart disease. Class 2 contains the "possible cardiacs," those without clear signs of severe injury. Class 3 includes those definitely without heart disease, the majority with cardiac neurosis or neuro-circulatory asthenia. Class 1 contains all the serious cases. These cannot be profitably divided into clearly bad and clearly good risks,⁶ a view directly opposite to that of the proponents of the functional classification. Active rheumatic fever, they state, definitely contraindicates pregnancy, but is rare in pregnancy. Another factor influencing prognosis is the age of the patient. In their group those 35 years of age or older were twice as likely to fail as those under 35. Schulze also reported that, of those over 35, 35% decompensated while only 20% of the younger group failed.

Stander⁵² also found the classification as to functional capacity unsatisfactory. He considers each patient an individual problem. Patients with no signs of decompensation who have gone through pregnancy comfortably are allowed to have spontaneous deliveries. With signs of cardiac strain in labor forceps are applied after full dilatation. With cardiac decompensation bed rest is advised with the usual therapy for heart failure. Upon the outcome of such treatment the decision as to operative delivery to lessen the strain of labor depends. He also divides patients into 3 groups. Group 1 includes those with a history of cardiac disturbances with the ability to carry on as usual, but without symptoms of decompensation. Group 2 contains those with no history of decompensation but who are forced to limit their activities. In Group 3, patients give a definite history of decompensation and incapacity in the past. In general, these call for radical treatment, interruption of pregnancy and possibly sterilization.

Although McIlroy and Rendel state that the actual anatomic lesion appears to have little bearing on the prognosis, they also state that cases with enlargement are less satisfactory than those without, and that cases with great enlargement and adhesive pericarditis are always serious. The past history may be a factor both in regard to a history of previous congestive failure and the type of acute rheumatic manifestation. All else being equal the history of a severe rheumatism or chorea makes the prognosis worse. Syphilitic aortic regurgitation is a dangerous lesion inside or outside of pregnancy because of the rapidity with which the functional capacity may change.

Lamb^{33a,b} does not believe that functional classification alone is sufficient for prognosis. In 110 patients studied, 12 patients in Classes 1 and 2-a became decompensated. Analysis of the cases led to the conclusion that the size of the heart, the presence of a long rumbling murmur

at the apex, the duration of the rheumatic disease and the signs of its activity, and the presence of auricular fibrillation were factors which must be considered as well in the evaluation of a pregnancy risk.

Pardee^{42b} lists 3 complications which affect the prognosis and modify treatment which would be based solely on functional capacity. Auricular fibrillation is often associated with embolic phenomena. This adds to the risk of labor and a patient in Class 2-b with auricular fibrillation should be allowed to continue pregnancy only if the heart rate can be kept in normal range with digitalis and if the exercise test does not cause prolonged and great tachycardia. In Class 2-a, the danger of emboli is not as bad as in Class 2-b but without similar control Cesarean section is preferred. Congenital heart disease and its complications have already been discussed. Bacterial endocarditis, the third special condition affecting prognosis, has also been considered.

It seems clear from the reports given that neither valvular defect alone, nor functional capacity alone is all important in prognosis. In general, functional capacity appears to be most important, but other factors also, cardiac enlargement, previous cardiac failure, auricular fibrillation, bacterial endocarditis, age, parity, rheumatic activity and certain types of congenital defects, among other factors, may play a part in prognosis. The middle ground appears to be the correct one. It is evident from the points of view just reviewed that, the diagnosis of organic heart disease being established or doubtful, the problem of prognosis is not simple. The divergence of views indicates how unsettled and insecure prognostication is, in spite of the advances in cardiology. To undertake the task of prediction of the course of the disease, so that a therapeutic approach most beneficial to both the mother and child will follow, requires decisions in an ill charted field of medicine where danger always lurks.

The late effects of pregnancy upon the functional capacity and cardiac reserve constitute a much debated and, at present, unsettled problem. Some believe that it shortens life, others that it does not. To throw light on this question, Gilchrist and Murray-Lyon²⁴ compared a group of cases who had borne children with a group who had not. They point out the fact that rheumatic heart disease itself runs a downward course over a period of years and that to show that pregnancy accelerates the process is not easy. The possibility that those with less severe degrees are selected for marriage and that women with the slightest defects are likely to bear more children adds further to the difficulties of analysis. Postmortem records of 109 cases, including males (40), nulliparous (28) and parous (41) females, were studied. All had mitral stenosis and died from cardiac causes. Average ages at death, correcting for deaths before marriageable age, were—males 39.3, nulliparous 42.1 and parous females 42.0, results which fail to establish the supposition that nulliparous women live longer than those who have borne children. In the females, the age at infection and duration of infection until death were not significantly different. It was also found to be unlikely that pregnancy played any significant rôle in the production of auricular fibrillation. These authors advisedly point out that the lack of differences in these groups does not disprove the injurious effects of child-bearing as all the figures are weighted in the reverse direction. Probably only the fitter patients marry, and if married only the fitter

are likely to have children. Moreover, those with large families are necessarily those who do not die early. If such a selection were true, those represented in the parous group might have lived longer had they borne no children.

Reid's^{43a} statistics for comparative ages at death of single and married women with rheumatic heart disease are similar to those just given. Hay and Hunt²⁸ doubt an added risk of pregnancy to the crippled heart with good reserve. Scott and Henderson⁴⁹ found that the average age at death of nulliparous females with rheumatic heart disease was 30 years (16 cases) while those with more than one pregnancy (14 cases) live on the average to the age of 40. A possible interpretation of such results has just been given. Surely child-bearing does not prolong life.

The statement is generally made that women with heart disease have easier and shorter labors than those without heart disease. Congestion with cervical softening is the usual cause assigned. Reis and Frankenthal's series bore out the contention of short labors. Nelson and Eades⁴¹ recently published data to the contrary. In Daichman and Kornfeld's series,¹³ labor in 82 primiparæ averaged 20.5 hours, longer than normal, and in 63 multiparæ 8.3 hours, a normal figure.

Mortality. Since treatment depends to such a great extent upon prognosis, and the rules governing prognosis are controversial, one can easily understand the wide diversity of opinion in the therapeutic procedures. Despite the fact that much remains to be done to clarify the procedures guiding the care of the gravido-cardiac, the efficacy of recent advances in prognostication and treatment is already reflected in mortality statistics. The uniformly grave prognosis of the older authors no longer holds.

It has been variously estimated that as high as 25% of maternal deaths are due to heart disease. From 1921 to 1931, 15.2% of all maternal deaths at Boston Lying-in Hospital were cardiac.⁶ In the 4 years previous the percentage reached 19. Reid,^{43b} comparing the reports of Boston Lying-in (1921-1927), New York Lying-in and the Robinson Memorial Hospitals, finds such striking differences as 17.2, 8.1 and 5.1%. Such differences are not geographical. Total deliveries in all 3 hospitals were 45,320, in which 480 deaths occurred. Of these 48 (10%) are ascribed to heart disease. In all the literature cited by Reid, the average mortality for cardiac diseases was 8.1% of the mortality for all causes. Scott and Henderson at Toronto General Hospital report 28 deaths in 5850 consecutive cases (0.43%). In 130 patients with rheumatic heart disease 11 (8.45%) died. In the last 41 cases, however, the rate was reduced to 2.33%. Daniels¹⁵ collected 1364 cases with a comparable maternal cardiac death rate of 49 (3.8%). Of 205 patients followed by Daichman and Kornfeld, 10 (4.87%) died. In 7670 patients of Reis and Frankenthal 21 died, 2 of these (9.52%) resulting from heart disease. Hanley and Anderson observed 3 deaths (5.5%) in 53 gravido-cardiacs.

Although these percentages vary greatly, probably because of differences in classification, they are much smaller than those of older reports, due in part to the better recognition of less serious grades of heart disease and to changes in treatment. The results of rigid prenatal care are striking. Schulze in 55 patients had one death (1.8%) in cases closely followed, while 12% occurred in cases not followed and in those

with severe decompensation. Bramwell⁴² noted only 8 deaths in 287 cardiac patients under medical supervision in the antenatal clinic. "When treatment is instituted as soon as the heart shows signs of beginning to fail, it is almost always successful." The ability to follow instructions is important. Carr and Hamilton state that cardiac deaths can be kept low. They found 32 fatal cases (6.4%) in 500 patients. Nearly $\frac{1}{2}$ of these patients were referred as emergencies and were not under the prenatal care of the hospital. Their mortality rate has fallen from 12% to approximately 3%. They estimate that in a community similar to theirs a good obstetrical hospital caring for the whole community would have a "natural" mortality rate of over 10% for its cardiac patients if the special requirements of these patients were not recognized and treated accordingly.

Comparatively little is written concerning fetal mortality in the gravido-cardiac patient. Carr and Hamilton found in 500 mothers, including those who had therapeutic abortion or who miscarried, 416 viable babies with a fetal mortality of 18%. In the entire clinic the fetal mortality was 1.3%. Teel⁵⁵ reported similar values. In 598 cases with 606 babies, the gross fetal loss was 20.13% and among the viable babies 7.28%. Without selection, therefore, cardiac patients have only 80% chance of having a baby that survives. These data justify his statement that the probability of obtaining a live baby should be an important factor in decisions on maternal risk. In delivery after the 35th week, the mortality was reduced to 3.91%. Premature mortality was higher than in those without heart disease, but this was not due to an undue proportion of prematures. The type of delivery appeared to be important. Of 15 babies delivered through the pelvis, 2 (13.33%) died. Of 15 delivered by Cesarean section, 73.33% died. In mature babies, however, fetal mortality in Cesarean section was low.

If congestive failure is absent, there is little danger of intrauterine death and pregnancy may be allowed to continue as far as the maternal condition permits.⁹² Delivery should not delay until congestive failure develops, for it is here that infant mortality rises to 80%. The fetal prognosis is better with delivery before the onset of cardiac decompensation regardless of the baby's weight. Clifford⁹³ also believes that the use of morphine within 4 hours of the delivery exerts a direct effect on the death rate of the infant. Teel agrees with Clifford that the greatest fetal loss is in a group with severe lesions, a group which could have been advised against pregnancy. In well compensated patients the fetal mortality is approximately that of the normal group. The procedure of choice, if the mother's condition permits, is to carry the pregnancy to the 36th week and deliver by the pelvic route. In compensated cases this permits normal delivery, possibly with low forceps. If, for maternal reasons, premature delivery is necessary, although Cesarean section means the poorest chance for the baby, Teel offers it as the method of choice.

Treatment.—The patient is to be treated as a cardiac patient with obstetrical complications. Much has already been said concerning treatment. This will not be repeated except to emphasize the fact that much confusion and differences of opinion abounds in the therapeutic field. Statistics are a guide of little value because of the great varia-

tions in the classification of cases. Individualization, the judgment of each case upon its own merits, is always foremost.

The routine procedures used in heart therapy, such as rest, digitalis, coronary dilators, the use of oxygen and dietary factors, do not constitute a part of this review. Additional rest and careful watching are necessary.

Prophylactic treatment, the prevention of pregnancy in poor risks, is a most important aspect of the problem. A clear history of congestive failure in the past, the presence of heart failure or auricular fibrillation and, less commonly, a complicating tuberculosis, nephritis or hypertension in the cardiac patient contraindicate pregnancy.⁶ Markedly reduced functional capacity of the heart, manifested in its later stages by congestive heart failure is usually a contraindication. A consideration of the circumstances leading to failure is important, however. Economic factors may play a most important rôle. If the patient gives a history of one therapeutic abortion because of heart disease and it can be determined that the functional capacity at that time was Class 2-b or 3, there is great danger of recurrence.^{42b} If it can be determined that the abortion was performed merely upon the basis of murmurs and not on estimation of functional capacity, it may be disregarded. To deny a woman the right to motherhood is an important decision. Mackenzie³⁵ stated that there was no single sign shown by the heart itself which would deny the right to motherhood. Religious factors may play a part. Reid states, "It is my opinion that there is too little faith in the heart's ability to carry on and too much radicalism in the treatment of cardiac patients who are pregnant." McIlroy and Rendel admonish that the obstetrical rule, "when in doubt do not interfere" applies equally well to the gravido-cardiac. No hard and fast rules can be laid down.

The effectiveness of rigid antepartum care with early detection of cardiac failure and immediate treatment has already been noted in the mortality statistics. A perusal of the statistics already given in the consideration of the functional capacity of the heart convinces one that a therapeutic approach formed basically upon that classification deserves prime consideration. The greater part of the following procedures is taken from Pardee's work.^{42b}

Those in Classes 1 and 2-a usually pass through pregnancy and labor with little difficulty. Congestive heart failure may develop quickly, however. Upper respiratory infection and over-exertion are the two most common precipitating causes. Patients must be warned of these factors. Infections are best treated with bed rest. The symptoms of early heart failure, ease of fatigue, dyspnea and cough, should be explained to the patient. Treatment of heart failure in its earliest stages is essential. Patients in Classes 1 and 2-a require little additional consideration. Their treatment is essentially that of the pregnant non-cardiac woman save for additional rest and careful watching both during pregnancy and labor. Increased respiratory or pulse rate in labor call for shortening of the second stage, usually by use of low forceps. Marchetti³⁷ admits them to the hospital 2 weeks before term and labor is spontaneous or with forceps if progress is not easy. Groups 2-b and 3 he admits 2 months or more before term. If improvement with treat-

ment is sufficient, they are permitted to enter labor with the use of forceps in the second stage. Without improvement he advises Cesarean section. Pardee divides the patients in Class 2-a in early pregnancy into two groups, those in 2-a before pregnancy and those reduced from 1 to 2-a in the early months. The latter group often improves and again passes into Class 1. The former group is not likely to develop cardiac insufficiency except, at times, in the later months. Treatment for heart failure is then necessary and rarely is abortion required except with lack of coöperation.

Patients in Class 2-b run a danger of serious cardiac strain in labor. This danger is more serious in Class 3. Patients in these two groups before the fourth month usually improve with bed rest and digitalis and only if improvement has stopped for 2 weeks should further procedures be entertained. If the patient has reverted to Class 2-a, careful supervision with complete coöperation may carry her through. Should she again fall into Class 2-b, Pardee advises Cesarean section. If she remains in Class 2-b, he thinks it best to interrupt pregnancy for fear of progression to Class 3. In those in Class 2-b with no improvement by treatment in the fifth, sixth, and seventh months, abortion is indicated, except (a) if the patient is anxious to have a child, (b) if expert guidance is at hand, (c) if the patient can coöperate and restrict her activity, and (d) if she is willing, should it become advisable, to have a Cesarean section before labor. Patients in Class 2-b throughout pregnancy with more severe cardiac insufficiency in the sixth and seventh months usually respond to bed rest and digitalis. Pardee does not interfere until no improvement results with 2 weeks' treatment. Then a decision is made as to their condition and ability to lead a sheltered life until viability. Those in Class 2-b with auricular fibrillation are not allowed to proceed unless the heart rate is well controlled with digitalis and the exercise test is satisfactory. The conditions are similar for fibrillation in Class 2-a.

Smith⁵¹ advises interruption for failure in the first 5 months and in the latter half of pregnancy his treatment is similar to Pardee's. Daichman and Kornfeld perform Cesarean section following compensation. Gilchrist advises Cesarean operation at or near term for those in Class 2-b before 6 months. If they enter this class later and respond to medical treatment he permits them to deliver themselves. Donovan¹⁸ advises therapeutic abortion in those with heart failure, cardiac reinfection and severe forms of aortic disease and congenital malformations. Although Carr and Hamilton state that they choose the method of delivery and anesthetic individually they usually deliver by Cesarean section (101 of 500 cases) those thought bad prospects for long labor and those definitely in failure. Bramwell⁴⁵ states that Cesarean section is well tolerated by cardiacs. The operation is generally described as causing less cardiac strain than pelvic delivery, particularly in primipare and secundipare. In the first 3 months, vaginal procedures do not disturb the circulation greatly, but in the fifth to seventh months the heart is less disturbed by abdominal operation.^{42b}

The favor of Cesarean section is not universal. DePuy¹⁷ states that it is not indicated except with complications that would require it. MacLennan feels that justification of Cesarean section is open to

question in patients in Class 2-b and more so in Class 3. Patients in Class 3 responds poorly to any form of treatment. Daly states that delivery from below after spontaneous labor with ether affords the easiest and best means of terminating labor in those patients who have no unfavorable obstetrical complications. Fitzgerald did not perform Cesarean section in his series. Corwin and his associates¹⁰ make no attempt to induce labor in the badly decompensated patient. Their much quoted formula is cardiac decompensation + forcible delivery = death. If compensation cannot be restored without delivery, the patient may die. With forcible delivery, they state, she will almost surely perish and it is best to trust to nature and let such cases deliver themselves with a short second stage and full ether anesthesia. In all cardiac patients delivered by the pelvic route, procedures to shorten the strain of the second stage are advisable. Low forceps following complete dilatation is the usual procedure.

Pardee feels that if cardiac insufficiency develops by the seventh month to the extent of requiring abortion, it is unlikely that the patient will ever again be able to go through pregnancy. Here he advises sterilization unless the economic factor has been important in preventing rest in pregnancy. Prolongation of the operation for sterilization is safe in Class 2-b but not in Class 3.

Rudolph⁴⁶ stresses the importance of posture during pregnancy and labor in that avoidance of the supine position is an important prophylactic measure in relieving extra strain upon the heart. He advises the sitting position during labor and the semirecumbent position during sleep in pregnancy.

There is no agreement as to the type of anesthesia preferred in the gravido-cardiac. Carr and Hamilton found it impossible to support by statistics a useful list of indications for choice of anesthesia. They avoid all drugs given by mouth or parietally except by inhalation because of the variations in dosage from patient to patient. In bad risks, dying while unconscious after these drugs have been given, one cannot tell how much of the collapse has been due to the drug. They prefer inhalation anesthesia with or without local. Ether, they state, is excellent for cardiacs when skillfully given. Others, as well, prefer ether.^{10,14,37,42a} They also use gas oxygen. The former or the latter, without preliminary medication and with local, if indicated, is their preference, except in prematures where ether is not used. McIlroy and Rendel speak well of gas but Pardee avoids it because of the increased cyanosis in an already strained circulatory system. He approves of local anesthesia in abdominal section. Herrmann and King state that spinal or local, even for Cesarean section, is by far the safest. Gilchrist obtained good results with spinal anesthesia. He emphasizes the statement that the anesthetist is more important than the anesthetic. Ware⁵⁷ finds that spinal anesthesia seems well suited for the pregnant woman with cardiac or renal complications. It permits a minimum of shock because of complete nerve block with muscle relaxation and introduces no element of renal or hepatic irritation. Furthermore, it adds nothing to the blood which may interfere with the resuscitation of the child.

Postpartum, it is advisable to keep the gravido-cardiac in bed at

least 3 weeks.⁴⁹ Congestive heart failure seldom occurs for the first time after delivery according to Carr and Hamilton. Schuman, however, reports 2 such cases. There appears to be a definite increase in the incidence of toxemias in cardiac patients.⁴⁴ Vascular collapse shortly after delivery may occur in such patients.¹

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PEDIATRICS

UNDER THE CHARGE OF
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CONGENITAL SYPHILIS.

SYPHILIS acquired before birth is known as congenital syphilis or hereditary syphilis. The former of these terms is preferable, as "hereditary syphilis" suggests too much and is misleading; for the transmission of syphilis does not follow any definite rule, such as is the case with the color of the eyes and hair, and similar familial characteristics.

According to Jeans and Cooke,¹⁰ there are several theoretical possibilities in the transmission of the infection to the child: "(1) Paternal germ transmission in which an infection already present in the spermatozoön is carried to the ovum during impregnation, with the development of an infected fetus; (2) Maternal germ transmission in which the infection originates in the ovum; (3) Postconceptional maternal transmission, which assumes an infection of the fetus from the mother during pregnancy through the placenta; (4) Parturitional maternal transmission, in which the infant is infected at the time of birth; (5) Acquired infection in the healthy infant after birth from contact with the virus containing lesions of parents or attendants." This last-named theory of infection is untenable as the means of transmission of congenital or hereditary syphilis, as the disease contracted in this manner would be of the acquired form regardless of whether the infecting individual was a relative or not. The parturitional maternal means of infection seems unlikely without some raw surface to serve as the atrium of infection and presupposes in addition spirochetæ-bearing lesions of the birth canal. The theories that the male or female germ cells may carry the infectious principle both formerly had their adherents; but it is doubtful if many would concede that these cells are capable of maintaining the spirochete within their unicellular protoplasm and yet of proceeding with normal fertilization. There remains but one theory of prenatal infection and that is the transmission of the infection to the infant from the maternal circulation by means of the placenta. Because this structure is impervious to the passage of microorganisms, the transmission must be accomplished by the implantation in large numbers of spirochetæ on the maternal side of the placenta with the infection later extending through to the fetal portion, and from there being taken up into the fetal blood circulation. This concept is supported by the finding of proliferative changes due to syphilitic infection in the placentas of syphilitic babies, and further by the fact that spirochetes are shown more readily on the maternal side of these placentas.

However, it is necessary for a spirochetemia to be present in the maternal circulation. Such a state exists in the primary and secondary stages of syphilis and if conception occurs during this period of the maternal infection, the conditions are ideal for placental infection. Pregnancy occurring during the tertiary stage of a syphilitic infection of the mother is very unlikely to result in fetal infection.

Veeder and Jeans²¹ say that in this connection must be mentioned the observation of Colles, who noted that the apparently healthy mothers of syphilitic children have an immunity to syphilis, or more correctly, do not contract syphilis when exposed to infection. It is now known that the apparently healthy mother is immune only because she has the disease in a latent form. The same authors mention the observation of Kassowitz, in 1876, that as a general rule the degree of transmissibility of syphilis to the offspring gradually diminishes in proportion to the duration of the disease. It was observed that in such families the first pregnancies ended in abortion, then came stillbirths and finally healthy children. In general, this rule is still correct although often exceptions occur even in instances where the modern antiluetic treatment has not been used. Of course where thorough and adequate antisyphilitic treatment is employed, healthy children are to be expected after the maternal serological test has become negative and remained negative for a sufficient interval.

Jarratt⁹ says that in congenital syphilis the infection is intrauterine and hence takes place by the blood stream through the placenta. In this no chancre or primary lesion occurs as it does in the acquired form, unless the changes in the placenta might be classified as such. He claims that this is the fundamental difference between congenital syphilis and the acquired form.

Syphilis is the cause of many premature and stillbirths. Litchfield⁴¹ asserts that there is justification in this statement especially if a positive Wassermann reaction is present in either parent. Stillbirths of 40 that showed records of the Wassermann reaction. Out of these 40 there were 6 which had a 4+ cord Wassermann; *i. e.*, 15% of the premature births that definitely were caused by syphilis. In addition to these 6 with positive cord Wassermans, 21 other cases of stillbirths were autopsied, and of these 9 were definitely syphilitic as evidenced by macroscopic and microscopic examination of the organs. Litchfield divides the lesions of congenital syphilis into two groups. In the first group they are present during fetal life and early infancy and are associated with a widespread general invasion over the body by the spirochæte. In some ways this is analogous to the secondary stage of acquired syphilis; but in fetal life there is no resistance and the infection is usually overwhelming. In the second group, the pathological changes occur in later childhood. These are the so-called late congenital lesions which are gummatous in character and correspond closely to the tertiary manifestations of acquired syphilis. This differentiation is only pathologic. It does not agree with the age, as the appearance of an early lesion may be deferred for several years or a condylomatous or gummatous lesion may be present at birth.

Schowalter¹⁶ also attributes congenital syphilis to syphilis of the mother. In a group of 6139 institutional children he found only 35 (0.56%), had a positive Wassermann reaction. This is a lower incidence than is reported by most observers. In the majority of cases, congenital syphilis cannot be detected by physical examination alone. It is astonishing the number of cases that are discovered only by routine Wassermann examinations. Where there is early involvement of the nervous system the disease can be detected only by a spinal fluid Wassermann test. In the presence of a positive spinal fluid Wassermann,

nervous system involvement must be admitted in spite of the absence of symptoms or other signs.

The symptomatology of congenital syphilis is variable. The time of onset of symptoms is also variable. Abt¹ points out that in the full-term baby congenital lues does not ordinarily manifest itself immediately after birth. The typical lesions may not appear until the third or the eighth week of life. In the premature or delicate and marantic baby the specific lesions of syphilis may appear during the first days of life. Snuffles or syphilitic coryza appear early. Syphilitic pemphigus, which occurs on the palms of the hands and the soles of the feet, is an early skin manifestation. The characteristic lesion of congenital syphilis is the diffuse infiltration of the skin. While wide areas may be involved the most frequent sites for the localization of this lesion is on the face or on the plantar surfaces. The spleen and the liver may show involvement. The long bones show typical disturbances of periosteal and endochondral ossification. Osteochondritis is one of the earliest syphilitic affections and may be observed during fetal life. Parrott's syphilitic pseudoparalysis is most frequently located in the wrist joint and is the result of a osteochondritis. Anemia, hydrocephalus, meningitis, encephalitis, endarteritis are among the other manifestations that may be encountered. In late congenital syphilis many signs and symptoms of the most diverse lesions are seen.

The determination of the presence of syphilis in the children of known syphilitic parentage is not easy. Sometimes it may be made by dark-field examination of scrapings from the umbilical vein taken at birth. Ingraham,^{8a} in his series by this means, detected syphilis in 19 of 87 living offspring of syphilitic mothers. He considered that his results were 100% accurate. At this age period of the infant other clinical criteria and laboratory aids are very unsuccessful. In spite of the results that he obtained negative dark field, examination does not rule out syphilis in the child but indicates the necessity of studying the infant by other methods. Parmalee and Halpern¹⁴ made a statistical study as to the comparative diagnostic value of clinical, roentgenologic and serologic observations. These show that of predominant importance are the roentgenologic evidence of osseous syphilis. During the new-born period there was suggestive clinical evidence in 23% and roentgenologic evidence in 44%. At 6 weeks of age the figures were 30, 8, and 61%, and at 3 months 25.7, 7.6 and 63% respectively.

Serologic diagnosis of congenital syphilis is often unreliable, and many syphilitic babies do not show clinical evidence of the disease. Bone involvement is a frequent form of specific involvement and these cases very often fail to show a positive Wassermann or other serologic reaction. Ingraham^{8b} studied the problem at the Philadelphia General Hospital for a year. Although the incidence of syphilis among the pregnant women was 11.8% and the majority of the women received insufficient prenatal antisymphilitic treatment to insure the birth of healthy children, not one of the 1517 babies discharged alive from the maternity ward showed any clinical evidence of congenital syphilis. The Wassermann reaction was positive only in 9 of 195 children of syphilitic mothers. The roentgenogram discovered 40 additional cases. In these, 26 (19.4%) were diagnosed before the age of 6 days, and 23 cases (17.1%) at ages of from 1 to 10 months. In all of these

cases the initial skeletal changes were evident roentgenographically before the blood serum gave a positive reaction. The early roentgenographic evidence is influenced by the treatment of the syphilitic mother before delivery. Of 51 cases in which the mothers were treated more than 2 months, in 5 (9.8%) syphilis was shown in the infants roentgenographically at 6 days. Of 68 cases in which the mothers were treated less than 2 months, in 21 (30.8%) there was positive roentgenographic evidence of syphilis in the babies. Those cases in which the Roentgen ray pictures revealed no positive evidence at the age of 6 days were studied again at the ages of 3 to 6 months. Of 36 cases adequately followed, in 12 (33%) the roentgenographic evidence subsequently became positive. In 3 cases serial Roentgen ray pictures were made of the same child taken over a period of several months. This leaves no reasonable doubt that the earlier bone changes seen a few days after birth are the precursors of the more advanced and easily recognized bone lesions which developed subsequently. The Wassermann reaction which originally was negative became positive as the disease progressed.

The unreliability of the usual Wassermann reaction is conceded by all observers. As has been indicated in the foregoing references, this test often fails to indicate the presence of syphilis while it is shown by Roentgen ray. On the other hand, according to Faber and Black,⁵ many of the positive Wassermann reactions in the newborn are not due to syphilis of the baby, but are the result of reagin transmitted from the syphilitic mother, thus giving a positive reaction in the blood of the child. They claim that antisyphilitic treatment is often given unnecessarily and to the detriment of the child. To obviate this the quantitative Wassermann test is recommended. They feel justified in withholding treatment in these and similar cases, first because no criterion remains for judging either the necessity of treatment or its results, and secondly because arsphenamine therapy has serious risks, to which the non-syphilitic individual should not be subjected. They claim that these risks are greater than those of failing to treat a possibly but improbably present latent infection. Their hypothesis in using the quantitative method was that with an initially positive reaction to a routine Wassermann test in an infant at or near the time of birth quantitative tests might reveal a progressive decline in titer to zero if syphilis were not present and the decline would be detectable considerably sooner than any change in the results of the ordinary routine test would be evident. If, on the other hand, the child were actually syphilitic, the titer would not decline and might even rise. If clinical signs of syphilis were absent and the titer was found to decline, treatment could be withheld safely, pending further observation.

The entire problem of syphilis is receiving governmental consideration. It well deserves recognition, because of the great toll it exacts in every phase of our national life, and is an important part of the program of the social security act of the Federal government. Measures for the control of this scourge are in preparation in the individual states of this country. Along this line a series of papers have been published by Vonderlehr,²² Smith,¹⁷ Moore,¹² Casselman,⁴ Stokes,¹⁹ and Nelson.¹³ The point in the syphilis control problem at which the attack upon congenital syphilis must be made is in the treatment of the syphilitic

expectant mother. Boas³ states that mothers with untreated syphilis always give birth to syphilitic children. In the treatment of the mothers he found that salvarsan gave very much better results than mercury. He recommends that every case of syphilis in pregnancy must be treated with salvarsan provided the patient can tolerate this treatment. It must be kept in mind that the kidneys at the termination of pregnancy are sometimes diseased. A careful examination of the urine must be made prior to each salvarsan treatment. Boas states that every syphilitic woman must be treated during pregnancy with salvarsan and mercury or bismuth, regardless of the age of her disease, of her previous treatment and of the result of her Wassermann reaction. In order to carry on the fight against congenital syphilis in an energetic manner, every pregnant woman, even though she has no history of syphilis and regards herself as uninfected, must be examined both clinically and serologically. When syphilis is diagnosed, she must be subjected as early as possible to an adequate and effective antisiphilitic régime. In cases where there is a syphilitic husband but it is not possible to prove an infection of the wife, many physicians insist on prophylactic treatment of the expectant mother.

Goldberg⁷ studied 653 cases of prenatal syphilis in seven clinics in New York City. He found that only 22.5% of these cases were put under treatment before the fifth month of pregnancy, though in one hospital a record of 37.5% was achieved. The antisiphilitic treatments administered to these women were possibly too few in number as 36.7% were given 5 treatments or less, and 56.3% had 9 treatments or less. In many instances blood tests were not repeated, and when they were done 3+ and 4+ findings were recorded in 169 instances (55%), and negative findings were recorded in 85 (28%). Of the cases in which complete records were available, there were 426 normal births and 45 losses, including 20 stillbirths, 13 premature, 6 deaths immediately after delivery and 6 macerated fetuses. There were 304 recorded blood tests of the newly born children, and of these 242 gave negative reactions, and 51 (16.7%) gave strongly positive reactions. The value of such tests made shortly after birth is questionable. The record of postpartum visits to the hospital in which confinement took place showed that 42.8% of these women failed to return and that 22.5% made only one visit. The record of visits of children born of these syphilitic mothers was comparatively high in one hospital with 71.7% returning for at least one visit. The record was very low in the other institutions. Records indicate that 46.6% of the women studied had passed through a non-fruitful pregnancy; of these 38% were of previous pregnancies while 8.6% were of the current pregnancy. Few living children of these mothers were given blood tests. Only 192 husbands were tested, and of these 28% were reported as positive for syphilis. This study showed the need for a more careful check of the mothers early in pregnancy and a thorough and rigid régime of antisiphilitic treatment of the mothers and a careful examination of the babies with active treatment of all positive cases.

Zakon²⁴ studied the effects of bismuth on the prevention of prenatal syphilis. He used bismuth salicylate in oil in 0.13 gm. doses, injected intramuscularly at weekly intervals throughout pregnancy. He used neoarsphenamine only in cases of bismuth intolerance or in cases of

early untreated syphilis. Under his care 26 pregnant syphilitic women who received this treatment gave birth to 26 full-term clinically healthy babies. There was no question as to the syphilis of the mothers, as all either gave positive serologic reactions or had a history of having received antisyphilitic treatment. The blood reactions of the children were studied as early as 2 weeks after birth and as late as 11 months of age. An effort was made to run two or more blood tests on the same child at various intervals. The serologic results were completely negative in 25 children and strongly positive in only 1 child. In 1 case the Kahn reaction was 1+ while the Wassermann was negative. In 3 cases the Wassermann alone was run because of insufficient serum. In all other cases the two readings were in complete agreement. Of the mothers only 6 received less than 6 bismuth injections; 21 patients received only bismuth while 5 received both bismuth and neoarsphenamine. Although no attempt was made to cure the syphilis in the mother, the maternal postpartum serology was improved in 13 patients in whom it became less positive or negative.

The active treatment of the syphilitic baby is the last but not the least important problem in congenital syphilis. The routine treatment as outlined by Yampolsky^{23b} is very thorough. A Wassermann test is made before and after treatment. Complete blood examination is made when possible before and after treatment. Roentgen ray examination of all long bones and of the fingers and toes are made before and after treatment. Urine specimens are examined at least twice during the course of the treatment. Temperatures are taken only if there is some suspicion of fever. Weight is recorded on every visit. Spinal puncture is performed and Wassermann test and globulin cell count are made on spinal fluid in every case at the end of the treatment.

Smith¹⁸ divides congenital syphilis into 3 age periods when lesions are most prevalent: from 1 to 6 months, from 6 to 8 years and at puberty. In the first period, the lesions are equivalent to those of early acquired syphilis, being chiefly ectodermal, mucocutaneous and osseous. All of these forms heal rapidly under not more than two courses of treatment. In the second period occur chiefly osteitis and periostitis, especially of the tibia and nasal septum, interstitial keratitis and occasionally nervous-system involvement. In the third period are common interstitial keratitis, eighth nerve deafness and neurosyphilis. Smith thinks that early congenital syphilis is curable. The start of treatment at an early age is an important factor together with the amount of treatment that is given in the first year. He feels that a baby whose treatment is started under 6 months of age has an 84% chance of serologic as well as clinical cure, if 50 injections are given before 2 years of age. The incidence of relapse increases with the age at which the treatment is started and decreases with the amount of treatment. Syphilis itself, except where the nervous system is involved, is rarely a cause of death in children over 6 months of age or in infants younger than 6 months who have had more than one course of treatment. All clinical manifestations of congenital syphilis respond to antisyphilitic treatment except neurosyphilis. In this form the condition may progress in spite of the treatment and even after the serologic reactions are negative.

In the treatment of the syphilitic baby bismuth, mercury and iodide as well as the various forms of arsphenamine have been used. Intravenous administration presents a difficulty that is not always surmountable; drugs which can be given intramuscularly are more readily used. The general trend of the treatment now is in the use of acetasone or stovarsol by mouth. Abt and Traisman² point out that of the 605 preparations with which Ehrlich worked before he arrived at the formula of salvarsan or 606, one was a preparation known to him as "594." This was regarded as unsuitable for intravenous usage. This preparation is acetylaminohydroxyphenylarsonic acid or acetasone; the French call it stovarsol and the Germans spirocid. It contains from 21.7 to 27.4% of arsenic. Abt and Traisman² used the following plan of administration: The first week, 0.005 gm. per kilo of body weight was given daily; the second week, 0.010 gm. per kilo daily; the third week, 0.015 gm. per kilo daily; and the fourth week, 0.020 gm. per kilo daily. This last was the maximum dose and it was continued for 5 more weeks, making a total treatment period of 9 weeks. This was followed by a rest period of 6 weeks. In small infants, the amount of drug ordered is crushed and dissolved in water and given a half hour before feeding. In older children, where the amount is greater, it may be divided into two or three doses.

Though one of the advantages of stovarsol or acetasone is that it could be given by mouth. Givan and Villa⁶ have used the drug intravenously in a series of 30 children with congenital syphilis. Acetasone was prepared by dissolving 1 gm. of the powder in 11 cc. of sterile distilled water to which has been added 9 cc. of normal (4%) sodium hydroxide. This amount of alkali has been proven to assure a solution of the highest tolerance upon intravenous injection. Thus the solution has been 1 gm. of acetasone to 20 cc. The dosage was started 0.3 gm. and gradually worked up to tolerance. The maximum dose was 1 gm. These injections were given at weekly intervals up to a maximum of 40 injections, and were always administered before meals. In every case there was improvement in the general condition of the patient with increase in weight and height. Improvement of active syphilitic lesions occurred in every case in which such lesions were present. Changes in serologic tests could not be evaluated in such a short period of observation. No urinary abnormalities were observed in this series, and the blood picture of every patient showed improvement. There was practically no untoward effect. One patient complained of nausea and vomiting after the sixth injection. The dosage was reduced to 0.3 gm. which she was able to tolerate well for 22 weeks. No dermatitis occurred. Although most of these cases had interstitial keratitis previously or when treatment was instituted, no visual complications were observed either of subjective or objective nature as a result of the drug. In this group several children who had not been able to tolerate neoarsphenamine were able to take acetasone intravenously without any untoward reactions. These observers feel that acetasone intravenously is one of the safe antisiphilitic remedies for use in the treatment of congenital syphilis.

Yampolsky²³ says that oral treatment of syphilitic children is coming into use, because the advantage of medication by mouth is the elimina-

tion of the difficulties of intravenous, intraperitoneal or other injection methods of syphilitic treatment. Although negro children show very little toxicity in the absorption of acetarsone, he warns us not to use the treatment indiscriminately because of the many reports of untoward effects. Because of the disappearance of cutaneous lesions and the general improvement this author feels that the oral use of acetarsone is of great value. He also found a favorable index in the serologic reactions and especially in the reversal of the Wassermann reactions in Wassermann-fast patients. He did not get very encouraging results as evidenced by roentgenologic changes. Yampolsky, in 1934, did not feel that definite knowledge was had on the status of acetarsone. He did not believe that the drug alone could cure syphilitic lesions of the bones and many other late lesions of congenital syphilis, although there was a place for acetarsone in the treatment of syphilis.

Traisman^{20a} says that acetarsone is the ideal drug for the oral treatment of congenital syphilis in the infant. In the older child it is also of great value. He thinks that in all probability better results may be obtained serologically if bismuth is given to the child during the 6 weeks rest interval between courses of acetarsone. The ideal method of dosage is that of Bratusch-Marrain in which the amount of acetarsone in grams consumed during one course of 9 weeks of treatment corresponds approximately to the weight of infants in kilograms. In this and in a previous contribution Traisman^{20b} observed very good results in the bone lesions of congenital syphilis as evidenced by the improvement in the Roentgen ray films.

Rosenbaum¹⁵ treated 100 cases of congenital syphilis with stovarsol. The serologic and clinical improvement was very good. He had toxic reactions in from 5 to a possible 8% of his cases, and they were usually mild in character. Serologic reversal was very much better with this drug than with the older methods of treatment.

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PHYSIOLOGY

PROCEEDINGS OF
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Subcortical Activities.—E. SPIEGEL (Department of Experimental Neurology, Temple University School of Medicine). The oscillations recorded in the electrocorticogram (ECoG) are not specific for the cerebral cortex. The electrothalamogram (EThG) and the electrocerebellogram (ECeG) show in the cat's brain slow and rapid waves quite similar to those of the ECoG. The slow waves of the EThG. may persist after elimination of corticofugal impulses or after transverse section of the midbrain; the amplitude and frequency of these waves, however, usually are diminished after these operations. With bipolar leads increase of the distance of the electrodes increases the amplitude of the slow waves. The depressive action of ether is not limited to the cortex but also noticeable on the EThG; the typical form of the electrothalamogram is preserved in sleep, as induced by dial; also in bulbocapnine catalepsy both types of waves are retained. Injection of strychnine in curarized animals increases the oscillations of the EThG. Sensory stimulation may induce slow deflections of the string, increase of the brief oscillations, as well a diminution of the slow waves of the EThG. The electrocorticogram picked up from a circumscribed cortical area (*e. g.*, sigmoid gyri) still shows slow waves after severance of the thalamocortical pathways and of nearly all connections with the rest of the cortex. The oscillations of the electrocerebellogram persist after transverse section of the midbrain; they are diminished but still present after severance of the afferent cerebellar tracts. Summation of rapid waves due to successive stimulation of cells in neuron chains may at least partly explain the genesis of the slow waves. The effects of sensory stimulation are explainable on the one hand by appearance of action potentials of the cells reached by the centripetal impulse, on the other hand by the interference between the sensory impulse and the wave circulating in the resting neuron chain.

The Cardiac Action of Thio-barbiturates.*—CHARLES M. GRUBER, with the assistance of CHARLES M. GRUBER, JR., and NICHOLAS COLOSI (Laboratory of Pharmacology, Jefferson Medical College). The experiments of this investigation were carried out on dogs, cats, rabbits, monkeys and terrapin. The excised terrapin auricles and ventricles were immersed in a bath of Locke's solution and the experimental drug added to this. On the dogs, cats and rabbits a series of experiments was performed in which only the blood pressure was recorded. In a second series of investigations, the blood pressure and the changes in

* This investigation was made possible by a grant from Parke, Davis & Co., to the Jefferson Medical College for research in science.

the action potential of the heart were studied simultaneously. A third series of experiments was performed on normal animals and this included also the monkeys, in which only the changes in the heart were studied with the electrocardiograph before and after the intravenous injection of thio-pentobarbital, thio-ethamyl and pentothal.

In the excised terrapin heart, irregularities in rate and force of both auricular and ventricular contractions were observed following the addition of the thio-barbiturate to the bath. These changes were not noted upon the addition of ortal sodium, sodium pentobarbital or sodium amytal.

In dogs, cats and rabbits, the first intravenous injection of the anesthetic dose of either thio-pentobarbital or pentothal caused a marked increase in the pulse pressure as recorded with a mercury manometer. This change, as revealed by the electrocardiogram, was found to be due to alternate premature and normal ventricular contractions. Following the premature contraction there was a long compensatory pause which is responsible for the widening of the blood pressure record. In about half of the experiments performed in which sodium thio-ethamyl was used similar findings were noted. In those few animals in which the first injection did not cause cardiac irregularity a second injection of either thio-ethamyl or thio-pentobarbital, after recovery from the anesthesia produced by the first injection, invariably caused marked irregularities of the heart including such changes as periods of paroxysmal ventricular tachycardia, alternate premature and normal ventricular contractions and decrease in the *P-R* intervals of the heart. The duration of this action varied in our experiments from 2 minutes to 35 minutes. In our experiments, irregularity of the monkey's heart was noted in those experiments in which 5 mg. per kg. of morphine sulphate had been previously administered. In both dogs and monkeys morphine enhanced the undesirable actions of sodium thio-pentobarbital, sodium thio-ethamyl and pentothal sodium on the heart. In some cases vagus stimulation abolished the irregular rhythm and in others established it. Large doses of atropine sulphate had no effect on this rhythm. In some experiments the injection of adrenalin chloride caused permanent disappearance of the irregularity but in other animals the disappearance was only temporary.

Inasmuch as repeated intravenous injections of sodium pentobarbital did not produce cardiac irregularities, it is assumed that the presence of the sulphur in the thio-barbiturate is responsible for the difference in action of the two drugs.

Comparative Permeability of Cells to Water and to Certain Solutes.
—BALDUIN LUCKÉ, H. K. HARTLINE, and R. A. RICCA (From the Laboratory of Pathology and the Johnson Foundation for Medical Physics, University of Pennsylvania). Only two types of cells have hitherto been used for most of the quantitative studies of cell permeability, namely, echinoderm egg cells and mammalian erythrocytes. In these two groups permeability is of an entirely different order, erythrocytes being many times more permeable. This difference raises the question whether the low permeability of echinoderm eggs is shared by corresponding cells of other invertebrate phyla, the differences between egg

cells and erythrocytes being a general one; or, conversely, whether the low permeability of echinoderm eggs is specific of this group only.

To answer this question search was made for suitable egg cells among other phyla of invertebrates. For accurate determination of permeability by the method we wished to use, cells should have the following characteristics: large numbers should be obtainable uninjured in an isolated state, they should be of readily measurable spherical shape, and, in any one animal, be of fairly uniform size; moreover, the cells should not be encased in a membrane so rigid as to oppose osmotic volume change.

We were able to find cells that satisfied these requirements in the annelid, *Chaetopterus* and the mollusc, *Cumingia*. Experiments were then designed to compare the permeability of these cells with that of corresponding cells of the echinoderm, *Arbacia*. The penetrating substances selected for this study were, first, water; second, the rapidly penetrating solute ethylene glycol; and third, the slowly penetrating glycerol.

Permeability to these substances was computed from measurements of the volume changes which take place when the cells are transferred from a medium with which they are in osmotic balance to a hypotonic or a hypertonic one. The cells were measured during the course of osmotic swelling or shrinking by means of a diffraction method, the details and advantages of which have been described in a previous communication (*J. Gen. Physiol.*, **19**, 1, 1935).

The results of the experiments may be summarized as follows:

1. The egg cells of *Chaetopterus* and of *Cumingia* are several times more permeable both to water and to the solutes studied than are the egg cells of *Arbacia*.

2. These differences in permeability are not correlated with the size of the cells.

3. Although there is considerable difference in permeability between the cells of *Chaetopterus* and *Cumingia* on the one side and of *Arbacia* on the other, the values are of the same order of magnitude and hence very low compared with the permeability of mammalian erythrocytes. It would therefore appear that the difference in permeability between these two groups of cells is probably of a general character.

4. Finally it may be pointed out that the three cells used are very favorable material for many kinds of studies on cell permeability: thus for rapidly penetrating substances the *Arbacia* cells is well adapted; while the more permeable cells of *Chaetopterus* or *Cumingia* are particularly suitable for studies of slowly penetrating substances.

The Action of Magnesium—Effect of Magnesium on Vascular Spasm.
—MITCHELL I. RUBIN and M. RAPOPORT (Children's Hospital, Philadelphia, and Department of Pediatrics, University of Pennsylvania). Since we had demonstrated in a previous experiment that magnesium prevented the contraction of sensitized smooth muscle both *in vivo* and *in vitro*, and with the evidence presented by McCollum and his associates, *viz.*, that rats on low magnesium diets showed phenomena suggesting vasoconstriction, it was decided to investigate the effect of diets high in magnesium on vasoconstriction produced in rats by the

intramuscular injection of ergotamine tartrate. It has been conclusively demonstrated that ergotamine tartrate produces vasoconstriction, and since hypertension is a manifestation of vasoconstriction, it was used as an index of the presence or absence of vascular spasm.

The normal blood pressure of our rats varied from 78 to 154 mm. of mercury. The average reading was 119, with a standard deviation of +19. Repeated readings for the same rat showed only a slight fluctuation (about 20 mm. of mercury).

One hundred twenty-eight rats were divided into two equal groups. One group was kept on the normal stock diet; the other group was fed the same diet with the addition of 2% magnesium carbonate. This level of magnesium carbonate in the diet did not interfere with normal body growth or normal bone growth. Following the injection of ergotamine tartrate (15 mg. per kg. of body weight, in 3 doses at weekly intervals) it was found that 94% of the rats on the magnesium diet failed to show hypertension, which was induced in 94% of the rats on the normal stock diet. Removal of the magnesium from the diet was followed by a rise in the blood pressure to hypertensive levels, and conversely, the addition of magnesium to the diets of the hypertensive rats on the normal diet resulted in a fall of the blood pressure to normal levels.

This experiment suggests the mechanism by which magnesium is effective in lowering the high blood pressure accompanying acute hemorrhagic nephritis. It further suggests that magnesium may be of therapeutic value in various vascular spastic states with or without hypertension.

ERRATUM

The A. M. A. Seal of Approval was inadvertently inserted in the Whooping Cough Pertussis Vaccine advertisement of The National Drug Company, in the December, 1936, issue of this publication, as the A. M. A. Council of Pharmacy has not accepted any Pertussis Vaccine.

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ORIGINAL ARTICLES.

INTENSIVE COLLAPSE THERAPY IN PULMONARY
TUBERCULOSIS:

I. A STUDY OF THE EXTENT AND RESULTS OF SUCH A PROGRAM
IN A GROUP OF 1124 PATIENTS.

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THE collapse therapy of pulmonary tuberculosis stands today at a level of statistical importance that provides convincing evidence of the immense strides made during the past few years in the selection and refinement of a variety of procedures. Its present status is also an index of the rapidly increasing recognition of its value by the medical profession. However, while there has been much in the literature of recent years concerning the excellent results to be obtained from collapse therapy, such accounts have dealt almost exclusively with the individual phases and methods of treatment. Statistics concerning the end results of a general and aggressively followed program of collapse therapy covering a large series of consecutively admitted patients, with minimal to hopeless involvement, and with all the possible varied indications for treatment, have been conspicuous by their absence from the literature.

The apparent explanation of this lack of information is that the general policy of considering all patients, whether or not having bilateral lesions, as possible candidates for some form of collapse therapy, is of comparatively recent origin. Except in a minority

of instances enough time has not yet elapsed to permit the accumulation of a sufficiently large series of patients so treated. The results in such a series of patients after several years of such treatment will much more accurately reflect the true value of collapse therapy than has previously been recorded in the literature for groups of discharged patients who have had mainly pneumothorax therapy alone in selected cases, or combined with one or two other operative procedures in a comparatively small percentage of the whole group.

In this, and in at least two subsequent papers, it is our intention to present a detailed analysis of the extensive and intensive program of collapse therapy which has been in operation at the Michigan State Sanatorium for a period of more than 5 years at the time of writing.

Scope of the Study. Including all patients in residence on June 1, 1930, and all admissions from this date to June 30, 1934, inclusive, 1666 patients are considered, of whom 542 had the childhood type of tuberculosis, extrapulmonary tuberculosis, non-tuberculous disease or no disease; the statistics presented in the various tables therefore cover a total of the remaining 1124 patients having the adult type of pulmonary tuberculosis. The statistics cover 424 males and 700 females, a few children being included. It is worthy of comment that by far too large a proportion of the 542 patients excluded from this study were found to have no disease or non-tuberculous disease following admission. This condition has been corrected almost entirely during the last 2 years of this period by a State Tuberculosis Commission ruling that whenever possible recent roentgenograms must be submitted with all applications for admission; this ruling has enabled us to conserve beds for patients in need of treatment. Incidentally, during the latter half of the 49-month period of this study, the capacity of the sanatorium was doubled to a total of 480 beds.

Two groupings have been made of the patients studied. During the period for which the end results were taken, 823 patients (302 men and 521 women) were discharged, while 301 patients (122 men and 179 women) remained in residence on January 1, 1935. The results of treatment in these two groups are considered both separately and together, but in the latter case only with regard to sputum and pulmonary cavity. The condition of the 301 resident patients was determined as of January 1, 1935, this date being arbitrarily chosen in order that no results should be tabulated in the case of any resident patient who had not been under treatment for a period of at least 6 months. The condition of all patients discharged up to this same date is given as of the date of discharge. To conform with the statistics given for the resident patients, both separate and combined tabulations are made for those discharged patients who were treated 6 months or more, and those who were treated for periods of from 1 day to 6 months. In the latter treatment period there are 186 patients, leaving 637 discharged and 301 resident patients who had treatment for 6 months or more. While this 6-month period was also arbitrarily chosen, it was felt that at least this much time must elapse before any of the permanent results of collapse therapy could be reasonably expected to manifest themselves clearly.

The entire course of treatment was not in every instance carried out at the State Sanatorium. Frequently patients are directly transferred from other institutions, with collapse therapy started before transfer. In these instances, when the previous period of treatment was uninterrupted to the date of transfer, and when the character of the treatment available to

patients in these institutions was considered to approximate the treatment policies at the State Sanatorium, all statistics, including all measures previously instituted to secure pulmonary collapse, were recorded as from the date of the previous admission to the end of the treatment period at Howell.

It is of considerable interest, and of relevant importance in estimating the results in the groups under review, to note the diagnostic classifications* of the patients at the time of admission. Of the entire group of 1124, the admission diagnosis was minimal in 105 (9.3%); moderately advanced in 365 (32.5%); far advanced in 654 (58.2%). For the 823 patients who were discharged, the corresponding figures at the time of admission were minimal 90 (10.9%); moderately advanced 263 (32%); far advanced 470 (57.1%).

For the year 1931, Miss Jessamine S. Whitney,³ Statistician of the National Tuberculosis Association, compiled general statistics dealing with tuberculosis hospitalization in the United States Registration Area. Figures giving the admission diagnosis of patients with pulmonary tuberculosis discharged during that year were compiled from the reports of 274 civilian sanatoria, covering a total of 36,665 patients. These figures are as follows: Minimal 16%; moderately advanced 30%; far advanced 54%. Comparing these figures with those for the discharge group in the present study, it will be seen that the State Sanatorium admitted 5% fewer minimal cases and 3% more far advanced cases than the average of other civilian sanatoria throughout the country. It is apparent, therefore, for purposes of comparison, that the final results of treatment indicated in Tables 1 and 2 cannot be considered to have been favorably influenced by the type of patient under treatment. In spite of the fact that an effort is made at this sanatorium not to admit patently hopeless cases, many of these, in addition to a large proportion of very far advanced patients for whom there is questionable hope of benefit from collapse therapy, find their way into our beds.

The large proportion of far advanced cases in the average admission totals for the country at large is very disappointing. There are many factors, of course, that account for these discouraging figures. Not the least of these is the tendency of the family physician (not invariably, it is true), and of the county officials, to concentrate their hospitalization efforts on the obviously hopeless or terminal patients, looking upon them as emergency cases in the light of the very apparent menace to all contacts. It is easy to forget that the moderately advanced ambulant patient, with one or two small cavities and positive sputum, and with many times the number of contacts, is undoubtedly much more of a menace to the community. The majority of such cases, moreover, can be ultimately arrested with proper and timely treatment. Such an argument, of course, would not apply if there were beds available for all

* The classification used is that of the National Tuberculosis Association, 1931.

active cases, for the question of segregation, even in the absence of hope of favorable response to treatment, is naturally one of great importance.

Condition on Discharge of 823 Patients (Table 1). The immediate proof of the success of sanatorium treatment is the classification which can be given the patient at the time of discharge, since obviously this is a measure of his ability to stand up under regulated activities, and is an index of his future chance of remaining in good health. These discharge standards, with the limitations imposed by hospital waiting lists, make impractical a classification of "apparently cured," which requires that conditions making possible a classification "arrested" shall have existed for a period of 2 years under ordinary conditions of life. On the other hand, a classification of "quiescent" implies incomplete treatment, as a rule more often the fault of the impatient individual than due to the failure of treatment. It is, therefore, apparent that the proportion of "arrested" and "apparently arrested" discharges must in the main be the measure of satisfactory treatment.

Of the 823 patients discharged, a total of 389 (47.3%) were arrested or apparently arrested; the quiescent and improved classifications totalled 163 (19.8%); 127 (15.4%) were unimproved; 144 patients (17.5%) died. Favorable results, from improvement to arrest, were secured in a total of 552 patients, 67.1% of the entire group.

A vital factor in obtaining these excellent discharge results was unquestionably the amount of collapse therapy employed. One or more measures of collapse were used in 72.3% of these 823 patients. Even this large percentage does not represent the entire extent of the application of collapse therapy to the patients at this institution. As will be explained later, we must also consider the 301 patients who were still in residence, since they are an integral part of the whole group of 1124 patients. Collapse therapy was employed for 886, or 78.8% of the entire group of 1124 patients in this study.

The next paragraph gives a revealing comparison of the figures above with those collected by Miss Whitney³ for the National Tuberculosis Association. The N.T.A. figures represent the results of treatment at the time of discharge of 41,972 patients from 278 civilian sanatoria in 1931. This large series of patients had a slightly better general prognosis than those of our study, and can be regarded as representative of treatment policies which, according to available reports, indicated that little more than 10% of all sanatorium patients throughout the country were receiving collapse therapy in that year.

The Michigan State Sanatorium figures compare with the National Tuberculosis Association³ figures as follows: Arrested and apparently arrested 47.3% and 17% respectively; quiescent and improved 19.8 and 41%; unimproved 15.4 and 19%; dead, 17.5 and 23%

respectively. Favorable results compared 67.1% and 58% respectively; use of collapse therapy 72.3 and from 10 to 15% respectively.

A closer analysis of these comparative figures shows that the most significant difference lies in the fact that in the State Sanatorium group of patients receiving 72.3% collapse therapy, it was possible to discharge more than 47% in the classification that most satisfactorily ensures future health protection and economic safety. This is an increase of nearly 200% over the arrested and apparently arrested classifications in the N.T.A. group, which received little collapse therapy. This is apparently a striking justification for the use of collapse therapy. The fact that the total of favorable results (improved, quiescent, apparently arrested and arrested) were 67.1% in our group and 58% in the N.T.A. group, a difference of only 9.1%, means little when these figures are properly analyzed. In our group, of the 552 patients in the columns representing favorable results (Table 1), 70% were arrested or apparently arrested. In the National Tuberculosis Association group, of 24,155 patients discharged with favorable results, only 29% of these were arrested or apparently arrested; 71% remained in the classifications affording a shaky prognosis after discharge.

It will be noted that the deaths in the 72.3% collapse therapy group are 5.5% less than in the N.T.A. group. This difference, while definitely in favor of the former group, is still not what it should be, for a very obvious reason. Previous to 1930 the status of collapse therapy at the State Sanatorium was essentially equivalent to the average elsewhere throughout the country. The considerable body of patients in residence had, except for those recently admitted, been for months to years under treatment without the benefit of the variety of eight different surgical measures that are now widely employed. This group furnished a far larger proportion of deaths and unfavorable results than the later admissions. In a sense they can be regarded as controls, in that it is not strictly true that all the patients in this study were equally fortunate in having proper collapse therapy available from the outset.

An analysis of the percentage of collapse therapy as distributed over the three admission classifications is particularly interesting, Table 1 showing its use in 43.4% of the 90 minimal patients, in 81.8% of the 263 moderately advanced, and in 72.6% of the 470 far advanced patients. Analyzed from another angle, of the 595 discharged patients who received collapse therapy, 39 (6.6%) had minimal involvement, 215 (36.1%) were moderately advanced, and 341 (57.3%) were far advanced at the time of admission.

Table 1 records the results of treatment both separately and combined for the three diagnostic classifications (minimal, moderately advanced and far advanced), and also compares the results in the 595 cases who received collapse therapy with the 228 who received none. Each of these classifications, for the recording of

the discharge condition, is treated in three groups, namely, the number of patients who were under treatment more than 6 months, those treated from 1 day up to 6 months, and the aggregate of the two. For proper interpretation of the table, it is essential to understand that in the "totals" column at the bottom of the table, each number represents a 100% complete treatment group which is subdivided in the corresponding sections above. The other tables are similarly arranged.

Of the group of 228 who received no surgery, it should be explained that among these patients we find the majority (51 of 90) of the minimal cases, with so trifling a degree of involvement that collapse therapy was considered unnecessary, and also those far advanced patients who were so hopelessly involved that collapse therapy was considered out of the question. In support of the latter statement we find that of the 129 far advanced patients in this non-surgical group, 56 were unimproved at the time of discharge, and 58 died, a total of 114, or 88.4%. Only 3 far advanced patients were arrested or apparently arrested. It will also be noted that 128 (56%) of these 228 patients remained in the sanatorium less than 6 months; whereas, of 595 patients in the surgical group, only 58, or less than 10%, remained less than 6 months. Of those in the non-surgical group staying less than 6 months, 81 were far advanced, and 78 of these (96.3%) were either unimproved or dead, the latter being the result for 43.2%. Of the entire non-surgical group, 61% were unimproved or dead, as compared with 22.2% of the surgical group, while 25.8% (32 of the 59 patients were minimal) were arrested or apparently arrested as compared with 55.4% of the surgical group. Further comparisons between the non-surgical and the surgical group may be misleading, since the results obviously are not to be explained by the character of the treatment, but rather by the type of material presenting itself for treatment.

We also find in this non-surgical group of 228 patients, in addition to those for whom surgery was unnecessary or inadvisable, a far larger relative proportion of those patients who, for various reasons, left the sanatorium against medical advice shortly after admission. There were 50 patients in this group discharged in such a manner, and it is worthy of note that only 2 of these had remained more than 6 months in the hospital. In these cases, although refusal of collapse therapy is rare among patients, discharge took place before therapy, which had been prescribed for many of them, could be instituted.

Of more significant interest is a comparison of the results of treatment in the groups of 39 minimal, 215 moderately advanced and 341 far advanced patients who received collapse therapy. Of the minimal cases, 84.7% were arrested or apparently arrested, with favorable results (improved to arrested) in 94.9%. None died and only 2 were unimproved. Corresponding figures for the total

of arrested and apparently arrested cases and for the total of favorable results among the moderately advanced patients were 72.1 and 93% respectively; among the far advanced patients, 41.6 and 66.2% respectively. Only one-third of the 341 far advanced patients failed to receive distinct benefit from surgery, while of the entire group of 595 surgical patients, only 22.2% were unimproved or dead, a smaller percentage than the deaths alone in the N.T.A.¹ totals from 278 sanatoria.

Table 1 also shows another striking fact. Among the far advanced patients who received surgery, 41.6%, as indicated above, were arrested or apparently arrested; of all the far advanced patients discharged, whether receiving collapse therapy or not, 30.9% were in the same classification; these percentages are respectively 145% and 82% greater than the corresponding figure of 17% for arrest and apparent arrest of cases discharged from the 278 civilian sanatoria, although the latter percentage has the immense advantage of including the minimal and moderately advanced cases with the far advanced.

It is to be expected, for the reasons already given, that the results in the surgical group alone should be better in each discharge classification than the corresponding figures for the combined surgical and non-surgical discharges. It is true that results in the non-surgical group are discounted from the standpoint of subject material for various reasons, but it must also be remembered that these results are considerably favored by the inclusion of 51 minimal cases. These minimal cases represent 22.4% of the non-surgical group, whereas the same classification represents only 6.6% of the surgical and 10.9% of the entire discharge group. With these factors in mind, the percentages for arrest or apparent arrest, and for the total of all favorable results, are 55.4 and 77.8, respectively, in the surgical group, as compared with percentages of 47.3 and 67.1 for the entire discharge group.

No statement in these pages is intended in any way to belittle the value of bed rest, or to suggest that collapse therapy is a substitute for it. The two are regarded as strictly complementary procedures, and bed rest is rigidly prescribed and maintained in order to consolidate the improvement afforded by collapse therapy. The favorable results obtained are attributable in large measure to the excellent morale of the patients in the acceptance of the rigid discipline which enforces bed rest. This morale, which also makes the refusal of prescribed collapse therapy an almost unknown occurrence, can only have been built up by continued observation on the part of the patients of the good results of such a course of treatment.

The criteria for all discharge classifications are based strictly upon the requirements of the National Tuberculosis Association standards. Although a glance at the exercise table in use at the Michigan State Sanatorium apparently does not indicate it, patients

fulfill the exercise requirements for arrested cases before they are placed in the highest exercise listing, Class XII. To encourage coöperation and the most convenient direction of the various exercise classes, a system has been devised involving the placing of numbered colored tags on the beds. It may be of interest to give the exercise listings below, as a number of requests for the table have been received from other sanatoria.

Class:	
Red Tag	I. Absolute bed rest. Patients to be washed, and if necessary, fed.
	II. Tray service. Bed bath. Toilet privileges allowed.
	III. Tray service. Toilet privileges. May take tub bath with assistance.
Green Tag	IV. One meal a day in main dining room. In addition to above privileges, to take bath without assistance.
	V. Two meals in dining room. May have bedside Occupational Therapy.
	VI. Three meals in dining room.
	VII. Dining room. Make own bed. May attend Church services and entertainments.
Yellow Tag	VIII. 15 minutes' exercise on level ground, or equivalent in Occupational Therapy department.
	IX. 30 minutes' exercise on level, or equivalent O. T.
	X. 45 minutes' exercise, or equivalent O. T.
	XI. One hour exercise, or equivalent O. T.
	XII. Extended exercise privileges.

This has proved to be a very satisfactory working system, and the bed tags make it easy to detect exercise violation. Certain minor modifications of these twelve classes are permitted at the discretion of the floor physician.

Cavity and Sputum Results of 823 Discharged Patients (Table 2). A necessary preliminary to the grooming of a patient for discharge is the closure of cavities and the conversion of positive sputum, where such conditions exist. Since, after these results have been secured, many patients leave the sanatorium before all exercise requirements are fulfilled, it is obvious that one can expect the percentages of cavity closure and sputum conversion to exceed the percentage of arrested and apparently arrested discharges. Many patients, therefore, for whom intensive collapse therapy has closed cavities and converted sputum, although discharged for various reasons as only improved or quiescent, can be classified in time as arrested or apparently cured, the lack of time for graduated exercise being the only obstacle to such a classification at the time of discharge.

Combined.

Non-surgical.

Surgical.

Period of treatment.

Cavities closed*	Over 6 mos. Under 6 mos.	1 1	100.0 100.0	116 4	95.1 36.4	202 2	68.0 8.0	319 7	76.0 18.9	2 ..	50.0 ..	6 ..	14.6 ..	8 ..	17.8 ..	1 1	100.0 100.0	118 4	93.7 23.5	208 2	61.5 1.9	397 7	70.3 5.8
	Total	2	100.0	120	90.2	204	63.4	326	71.3	2	20.0	6	5.0	8	6.2	2	100.0	122	85.3	210	47.6	334	57.0
	Over 6 mos. Under 6 mos.	2 3	1.6 27.2	40 14	13.5 56.0	42 17	10.0 46.0	1 ..	25.0 ..	7 ..	17.1 9.0	8 7	17.8 8.3	3 3	2.4 17.7	47 21	13.9 20.4	50 24	10.8 19.8
Cavities decreased	Total	5	3.8	54	16.8	59	12.9	1	10.0	14	11.8	15	11.6	..	6	4.2	68	15.4	74	12.6	
	Over 6 mos. Under 6 mos.	4 4	3.3 36.4	55 9	18.5 36.0	59 13	14.0 35.1	1 6	25.0 100.0	28 71	68.3 91.0	29 77	64.4 91.7	5 10	3.9 58.8	83 80	24.6 77.7	88 90	18.9 74.4	
	Total	8	6.0	64	19.8	72	15.8	7	70.0	99	83.2	106	82.2	..	15	10.5	163	37.0	178	30.4	
Totals	Over 6 mos. Under 6 mos.	1 1	100.0 100.0	122 11	100.0 100.0	297 25	100.0 100.0	420 37	100.0 100.0	4 6	100.0 100.0	41 78	100.0 100.0	45 84	100.0 100.0	1 1	100.0 100.0	126 17	100.0 100.0	338 103	100.0 100.0	465 121	100.0 100.0
	Total	2	100.0	133	100.0	322	100.0	457	100.0	10	100.0	119	100.0	129	100.0	2	100.0	143	100.0	441	100.0	556	100.0
	Over 6 mos. Under 6 mos.	5 1	14.3 25.0	108 5	56.5 20.8	204 4	65.6 13.3	317 10	59.0 17.2	2 2	8.7 7.1	4 2	13.8 10.5	9 1	18.8 1.2	15 5	15.0 3.9	7 3	12.1 9.4	112 7	50.9 16.3	213 5	59.3 4.5	332 15	52.1 8.1
Sputum becoming negative†	Total	6	15.4	113	52.6	208	61.0	327	54.9	4	7.8	6	12.5	10	7.8	20	8.8	10	11.1	119	45.3	218	46.4	347	42.2
	Over 6 mos. Under 6 mos.	30 3	85.7 75.0	76 12	39.8 50.0	19 5	6.1 16.7	125 20	23.3 34.5	21 25	91.3 89.3	23 14	79.3 73.7	3 4	6.2 5.0	47 43	47.0 33.6	51 28	87.9 87.5	99 26	45.0 60.5	22 9	6.1 8.1	172 63	27.0 33.9
	Total	33	84.6	88	40.9	24	7.1	145	24.4	46	90.2	37	77.1	7	5.4	90	39.5	79	87.8	125	47.5	31	6.6	235	28.5
Sputum remaining positive‡	Over 6 mos. Under 6 mos.	7 7	3.7 29.2	88 21	28.3 70.0	95 28	17.7 48.3	.. 1	3.6 ..	2 3	6.9 15.8	36 76	75.0 93.8	38 80	38.0 62.5	.. 1	9 10	4.1 23.2	124 97	34.6 87.4	133 108	20.9 58.0	
	Total	14	6.5	109	31.9	123	20.7	1	2.0	5	10.4	112	86.8	118	51.7	1	1.1	19	7.2	221	47.0	241	29.3
	Over 6 mos. Under 6 mos.	35 4	100.0 100.0	191 24	100.0 100.0	311 30	100.0 100.0	537 58	100.0 100.0	23 28	100.0 100.0	29 19	100.0 100.0	48 81	100.0 100.0	100 128	100.0 100.0	58 32	100.0 100.0	220 43	100.0 100.0	359 111	100.0 186	637 100.0	100.0 100.0
Totals	Total	39	100.0	215	100.0	341	100.0	595	100.0	51	100.0	48	100.0	129	100.0	228	100.0	90	190.0	263	100.0	470	100.0	823	100.0

* Refers to the total of all cavities, whether present on admission or developed subsequently. Any minimal cases included refer to development of cavity during treatment.

† Includes patients with negative sputum on admission, who developed positive sputum during treatment, and finally became negative.

‡ Includes patients with negative sputum on admission, who developed positive sputum during treatment, and were still positive at the time of discharge.

Table 2 reveals that of the 823 patients in the discharged series, 586 (71.2%) had cavities, and, of these, 457 had some form of collapse therapy. In this surgically treated group, 71.3% of the cavities were closed, while favorable results were secured in a total of 84.2%. In the 133 moderately advanced patients, cavity closure was effected in 90.2%, and favorable results in 94%. Corresponding figures for the 322 far advanced patients were 63.4 and 80.2% respectively. It will be noted that only 2 minimal patients developed a cavity following admission, and that both of these were successfully treated. This fact seems to be of peculiar significance, since nearly half of our minimal patients receive at least phrenic surgery.

It will be further noted that of the 457 surgically treated cavity cases, only 37 were under treatment less than 6 months, and, of these, 18.9% had their cavities closed. Further study of Table 2 reveals that 420 patients, or 91.9% of the surgical group, remained more than 6 months, as compared with only 34.9% of the non-surgical group of 129 cavity cases. Because these facts regarding hospitalization periods may be misunderstood, it should be noted that in the non-surgical group there were only 10 moderately advanced patients, and the poor admission prognosis of the remainder is indicated by the fact that, of 119 far advanced cavity cases, treatment failed in 99. However, Table 1, which lists all discharges without respect to cavity, shows also, as pointed out before, that more than 90% of the 595 surgical cases remained more than 6 months as against 43.9% of the non-surgical group. These figures have led us to another conclusion, namely, that collapse therapy must of necessity increase the average per patient hospitalization period in any institution where the majority of patients are far advanced, and where the pernicious and wasteful practice of a limited hospital stay can be avoided. This somewhat paradoxical statement should be modified by the explanation that, while it is undoubtedly true that collapse therapy shortens the stay of most minimal and moderately advanced cases, it has the opposite effect in the majority of the far advanced cases amenable to surgery, a large proportion of whom have, at the time of admission, a questionable to poor prognosis. Many patients, who would otherwise die not long after admission, finally become arrested or apparently arrested through collapse therapy, although frequently several years are required to effect this otherwise unobtainable result. There is certainly nothing in the literature that approaches the results in Table 1, showing 41.6% arrested and apparently arrested of the far advanced patients who received surgery. These results could not be secured without surgery. Incidentally, the number of far advanced patients who die or are discharged within a comparatively short period cuts the average hospital stay of this group down toward that of the moderately advanced group. In support of the contention that an extended hospitalization should be the rule if

at all possible, is the statement by Whitney and Myers,⁴ after a follow-up study of 7000 discharged patients, that the length of sanatorium treatment is directly reflected in the postsanatorium history of far advanced patients.

Of the entire group of 586 cavity cases, 57% were discharged with cavities closed, and a total of 69.6% with favorable results. These figures compare unfavorably with those of 71.3 and 84.2, respectively, for the 457 cavity cases treated with surgery, but Table 2 shows in explanation that of the non-surgical cavity cases, only 6.2% had cavity closure, while 106 (82.2%) of the same non-surgical group of 129 either died or were discharged with cavities unaffected or increased in extent. (To avoid misunderstanding, it should be mentioned that all statistics cited for closure of cavities indicate complete closure of all cavities, whether single or multiple, and whether in one or both lungs. Should a small subsequently developed cavity remain, even though all original cavities were closed, the result is interpreted as partial only, and placed under "cavities decreased.")

No statistics are tabulated in this study which correlate the sputum results with direct respect to the existence or non-existence of cavities. These results are given separately, in Table 2, for the entire group of 823 discharged patients. It is interesting to note that 87.8% of the 90 minimal cases and 47.5% of the 263 moderately advanced patients remained sputum negative throughout the period of treatment, while 47% of the 470 far advanced patients remained sputum positive. Treatment eliminated bacilli from the sputum in 42.2% of the 823 discharged patients. Grouping these with patients whose sputum was negative throughout, 70.7% of the patients were discharged with negative sputum. Represented in another and more pertinent way, 588 patients were sputum positive at some time during treatment, of which total 347 (59%) had sputum conversion. There were 439 far advanced patients among these 588, and 49.7% of these responded satisfactorily to treatment. Of the 138 moderately advanced patients with positive sputum, conversion was effected in 119 (86.2%).

A consideration of the sputum results in the group of 595 surgically treated cases reveals a far better story, 54.9% of these being discharged with sputum converted from positive to negative. Since 24.4% remained negative throughout, this represents a total of 79.3% discharged with negative sputum. Here again the efficacy of surgical treatment is better shown by the fact that, as calculated from Table 2, in a total of 450 patients with positive sputum, conversion was effected in 327 (72.7%). There were 317 far advanced patients among the 450, with bacilli elimination in 65.6%. Of the 127 moderately advanced patients with positive sputum, surgery eliminated bacilli from 113 (89%). Further study of the table shows that of the 595 surgically treated cases, 100% of the 39 minimal

patients, 93.5% of the 215 moderately advanced, and 68.1% of the 341 far advanced patients, were discharged with negative sputum.

For the purpose of this study, patients were arbitrarily placed in the sputum negative group who had not had tubercle bacilli in their sputum for a period of 2 months previous to discharge. Lest this seem a rather short period for this classification, a close check revealed that only 37 of the 823 discharged patients had a positive sputum as recently as 4 months previous to discharge, and this in the face of a searching sputum routine of perhaps above average severity. The present laboratory routine calls for three smear examinations upon admission, and if these are negative, a 24-hour concentrate is examined. This is repeated in the second month, and, if still negative, a culture is planted. The routine for all other patients, formerly positive or not, calls for 2 smear examinations monthly. If the sixth smear is still negative, 2 concentrates follow and then a culture. This procedure is repeated over the next 3-month period. While this exact routine was adopted only during the latter part of the study period, 2 routine monthly smears, interspersed with long series of concentrate studies and frequent cultures, were the rule during the entire period, and particularly as a preliminary to discharge.

Results for 301 Resident Patients (Table 3). The results of treatment of the 301 patients who had been resident for 6 months or more are extremely interesting, although treatment was incomplete at the time of study. Collapse therapy was administered to 291 (96.7%) of this group. The explanation of this amazingly high percentage of surgery undoubtedly lies in the fact that no resident patients were included in the study who had less than 6 months treatment. In this resident group there were, therefore, left only 15 minimal patients, of whom 13 received surgery, while of the 184 far advanced patients, only 4 remained who were apparently too hopeless for surgery. Also, since during the last 2 years of this period of study there has been a considerable increase in the number of major operations, and because it is a general rule to keep all thoracoplasty patients strictly in bed for 6 months before permitting exercise privileges, a larger proportion of these resident patients therefore fall into the major operative group than is found in the discharged group of 823. These facts explain why some of the cavity and sputum results in Table 3 are better than those in Table 2, and we have reason to believe that when the last of the 1124 patients in this study have been discharged, the discharge results will be even more satisfactory than Tables 1 and 2 indicate.

The percentages of minimal, moderately advanced and far advanced patients in this resident group were 5, 33.9, and 61.1, respectively. Of the 301 patients, 245 (81.4%) as compared with 71.2% of the discharged group, had cavities, and all but 3 received collapse therapy. In this surgical group of 242 patients, 71.9%

TABLE 3.—CAVITY AND SPUTUM RESULTS OF 301 RESIDENT PATIENTS.

	Surgical.						Non-surgical.						Combined.					
	Minimal.		Mod. adv.		Far adv.		Combined.		Minimal.		Mod. adv.		Far adv.		Combined.		Minimal.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Cavities closed*	3	100.0	59	86.8	112	65.5	174	71.9	1	100.0	1	33.3	3	100.0
Cavities decreased	6	8.8	49	28.7	55	22.7	2	100.0	2	100.0	2	66.7
Cavities unchanged or increased	3	4.4	10	5.8	13	5.4
Totals	3	100.0	68	100.0	171	100.0	242	100.0	1	100.0	2	100.0	3	100.0	3	100.0
Sputum becoming negative*	3	23.1	49	50.0	110	61.1	162	55.7	3	20.0
Sputum remaining negative	10	76.9	35	35.7	15	8.3	60	20.0	2	100.0	4	100.0	1	25.0	7	70.0	12	80.0
Sputum remaining positive*	14	14.3	55	30.6	69	23.7	3	75.0	3	30.0
Totals	13	100.0	98	100.0	180	100.0	201	100.0	2	100.0	4	100.0	4	100.0	10	100.0	15	100.0
																	102	100.0
																	181	100.0
																	301	100.0

* See notes at bottom of Table 2.

TABLE 4.—CAVITY AND SPUTUM RESULTS OF 1124 CONSECUTIVELY ADMITTED PATIENTS.

Period of treatment.	Surgical.						Non-surgical.						Combined.					
	Minimal.		Mod. adv.		Far adv.		Minimal.		Mod. adv.		Far adv.		Minimal.		Mod. adv.		Far adv.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Cavities closed*	Over 6 mos.	4	100.0	175	92.1	314	67.1	493	74.5
	Under 6 mos.	1	100.0	4	36.4	2	8.0	7	18.9
	Total	5	100.0	179	89.0	316	64.1	500	71.5
Cavities decreased	Over 6 mos.	8	4.2	89	19.0	97	14.6
	Under 6 mos.	3	27.2	14	56.0	17	46.0
	Total	11	5.5	103	20.9	114	16.3
Cavities unchanged or increased	Over 6 mos.	7	3.7	65	13.9	72	10.9
	Under 6 mos.	4	36.4	9	36.0	13	35.1
	Total	11	5.5	74	15.0	85	12.2
Totals	Over 6 mos.	4	100.0	190	100.0	408	100.0	662	100.0
	Under 6 mos.	1	100.0	11	100.0	25	100.0	37	100.0
	Total	5	100.0	201	100.0	493	100.0	699	100.0
Sputum becoming negative*	Over 6 mos.	8	16.7	157	51.3	314	64.0	479	57.9	2	8.0	4	12.1	9	17.3	15	13.6	..
	Under 6 mos.	1	25.0	5	20.8	4	13.3	10	17.2	2	7.1	2	10.5	1	1.2	5	3.9	..
	Total	9	17.3	162	51.8	318	61.0	489	55.2	4	7.5	6	11.6	10	7.5	20	8.4	..
Sputum remaining negative	Over 6 mos.	40	83.3	111	38.1	31	6.9	185	22.3	23	92.0	27	81.8	4	7.7	51	49.1	..
	Under 6 mos.	3	75.0	12	50.0	5	16.7	20	34.5	25	89.3	11	73.7	4	5.0	43	33.6	..
	Total	43	82.7	123	39.3	39	7.5	205	23.1	48	90.6	41	78.8	8	6.0	97	40.8	..
Sputum remaining positive*	Over 6 mos.	21	7.3	143	29.1	164	19.8	2	6.1	39	75.0	41	37.3	..
	Under 6 mos.	7	29.2	21	70.0	28	48.3	1	3.6	3	15.8	76	93.8	80	62.5	..
	Total	28	8.9	164	31.5	192	21.7	1	1.9	5	9.6	115	86.5	121	50.8	..
Totals	Over 6 mos.	18	100.0	289	100.0	191	100.0	828	100.0	25	100.0	33	100.0	52	100.0	110	100.0	..
	Under 6 mos.	1	100.0	21	100.0	30	100.0	58	100.0	28	100.0	19	100.0	81	100.0	128	100.0	..
	Total	52	100.0	313	100.0	521	100.0	886	100.0	53	100.0	52	100.0	133	100.0	238	100.0	..

* See notes at bottom of Table 2.

had their cavities closed, and favorable results were obtained in a total of 94.6%. These figures compare with 71.3 and 84.2%, respectively, of the discharged patients who received surgery. The difference in the percentages of favorable results in the discharged group and in the resident group is apparently due to the number of surgical patients who were discharged within 6 months following surgery, plus those discharged in the early part of this 5-year period, for whom the major collapse therapy program was relatively less intensive. It will be noted that, in the treatment of the resident patients with cavity, favorable results were secured in from 94 to 100% of the three classifications who were treated surgically. These percentage results were practically the same for the entire group of 245 patients, since only 3 cavity cases did not receive surgery.

The sputum results are likewise very satisfactory, the same criteria ruling here as for the discharge group. Of the surgically treated group (291 of 301) the sputum was, at the arbitrary date of January 1, 1935, negative in 100% of the minimal patients, 85.7% of the moderately advanced, and 69.4% of the far advanced patients, or 76.3% of the entire group. Expressed in a more significant way, of the 231 surgically treated patients who had positive sputum when admitted or subsequently, conversion was effected in 70.1%. Corresponding figures for sputum conversion for the 3 minimal, 63 moderately advanced and 165 far advanced patients with positive sputum, were 100, 78.8 and 66.7%, respectively.

Results for 1124 Patients (Table 4). The combined results for sputum and cavity closure for the entire series of 1124 patients in the study are in some respects better than for the discharged group alone. Others figures in Table 4 more truly reflect the extent of application of collapse therapy to patients as consecutively admitted. For example, the percentages of collapse therapy for the 105 minimal, 365 moderately advanced and 654 far advanced patients were 49.5, 85.8 and 79.7, respectively, as compared with percentages of 43.3, 81.8, and 72.6, respectively, for the 823 discharged patients. Collapse therapy was instituted in 78.8% of the entire series of 1124 patients, as compared with 72.3% of the discharge group of 823. In addition to the 886 who actually received surgery, pneumothorax was recommended and attempted unsuccessfully, with no subsequent surgery being done for various reasons, in a further group of 24, making a total of 910 patients with collapse therapy indications, or 81% of the patients in this study.

A subsequent paper will go into more detail concerning anatomic and pathologic features of the cavity results in this series. Table 4 is a summation of Tables 2 and 3, but of particular interest in the comparison of its figures for consecutively treated patients as compared with the figures for a (Table 2) discharge group. The percentage of cases with cavity is higher than in Table 2, namely, 831 patients (73.9%) as compared with 586 patients (71.2%). In the

entire series of 1124 patients, 84.1% of the cavity cases received collapse therapy as compared with 77.9% in the discharged group. Five of the 105 minimal cases developed cavity following admission, and all closed with surgery, while 89% of the moderately advanced and 64.1% of the far advanced patients were likewise treated successfully. Favorable results, including decrease in size of cavities following surgery, were obtained in 94.5% of the moderately advanced and in 85% of the far advanced patients, the latter figure being approximately 5% better than for the discharge group.

For the entire surgically treated cavity group of 699 (Table 4), closure was effected in 71.5% of cases, and favorable results secured in 87.8%. For the combined surgical and unaided bed rest total of 831 cavity cases, percentages for closure and favorable results were 61.2 and 77, respectively. As an indication of the desperate prognosis at the time of admission of the 132 cavity cases receiving bed rest alone, 121 of these were far advanced, of whom only 6 had final closure of cavities.

Of the 1124 patients 822 had positive sputum either at the time of admission or subsequently; 509 (61.9%) of these were converted into negative sputum cases. This group of 509 represented 45.3% of all patients, and, with the 302 who remained negative throughout, the entire negative sputum group totalled 72.2%. The sputum remained positive in 279, or 42.7% of the 654 far advanced patients; it should be noted that this group includes 115 of the 133 far advanced patients who received no surgery.

The sputum results in the surgical group alone are, of course, much better, 78.3% in all having become sputum negative, while of the 681 patients who had positive sputum, conversion was obtained in 71.8%. Distributed over the three admission classifications, conversion was effected in 66% of the 482 far advanced patients, in 85.3% of the 190 moderately advanced, and in 100% of the minimal patients who had positive sputum on admission or subsequently. All of the minimal cases, 91.1% of the moderately advanced, and 68.5% of the far advanced patients in the surgical group of 886 eventually became sputum negative.

Analysis of Deaths. A separate study was made of factors having both an academic and causal relationship to the 144 deaths in the series, which represents 17.5% of the discharges, or 12.8% of the entire group studied. Collapse therapy was instituted in 85 of these patients, of whom 70 (82.4%) remained under treatment more than 6 months; of the 59 who received no collapse therapy, only 38.9% remained 6 months or more. Of the entire group, 81 (56.3%) were under treatment less than 1 year.

A prognosis is recorded for each patient at the time of the first staff conference, within a few days of admission. Six prognoses are used: Hopeless, poor, questionable, fair, good and excellent. It is significant, as indicating the type of case expected to respond

to therapy, that the best prognosis given any of these 144 patients on admission was fair; less than 10% were so classified; 18.1% were regarded as hopeless cases; 49.3% had a poor prognosis; 22.9% were at the best regarded as having a questionable chance for recovery. A total of 90.3%, therefore, had a grave outlook from the first. The admission classification was far advanced for 137 (95.1%) of the 144 deaths. All except 11 of these patients had cavities when admitted, and nearly 50% had bilateral cavitation. At the time of death, 66.7% of the far advanced cavity patients had bilateral cavities. It is of further interest to note that of 131 patients (including 5 of 7 moderately advanced) with cavity on admission, 26% had one or more cavities 6 cm. or more in diameter, and 5.3% had cavities exceeding 12 cm.

Excluding pneumothorax and phrenic nerve surgery, 33 patients, or 22.9% of all the deaths, received major thoracic surgery. Of these, 19 were regarded as postoperative deaths, in that death occurred within an arbitrarily set period of 2 months following operation, regardless of the immediate causative factor. One patient died following operation for renal calculus; 7 deaths were due to causes other than tuberculosis; 117 died of progressive extension of the disease. Therefore, 81.2% of the deaths were due to progressive tuberculosis, and 13.2% to thoracic surgery.

Comment. Perhaps one of the most conclusive arguments in favor of the aggressive use of collapse therapy in the treatment of pulmonary tuberculosis is the amazing evolution of this form of treatment over the entire country during the past 4 years. In contrast with the figures prevailing at the time of the Whitney³ report for 1931 is the report of the Committee on Treatment¹ of the American Sanatorium Association for 1933, tabulated from responses to questionnaires sent to 112 institutions located in 35 states and 1 territory. This report, covering 29,211 patients, indicated that 39% received some form of collapse therapy, with nearly 24% of the institutions reporting an incidence of more than 50%, 2 reporting 80% or more, and only 13 institutions reporting 10% or less of patients receiving such therapy. It is possible, of course, that this report, confined to 29,211 patients in 112 institutions, which undoubtedly include the majority of institutions most advanced in collapse therapy, might represent a higher average of collapse therapy than was actually being done throughout the whole country in 1933. The National Tuberculosis Association report for 1931 covered 274 civilian sanatoria with a total of 36,665 patients. In 1933, there were actually more than 400 institutions operated exclusively for tuberculosis in the United States, exclusive of preventoria and tuberculosis departments. Nevertheless, the figures of the American Sanatorium Association indicate a marked increase in the percentage of collapse therapy in use over indicated conditions

in 1931, and this picture has, without question, undergone a further favorable change in the interval since 1933.

Of the 112 institutions in this report, 64 confined their collapse therapy program to three measures, pneumothorax, phrenic nerve surgery, and thoracoplasty. It is obvious that many patients for whom the first two procedures have failed, may not be suitable candidates for thoracoplasty. We believe that the very satisfactory final treatment results reported in our study are in no small measure due to the availability of other alternate procedures, such as intrapleural and extrapleural pneumonolysis, scalenectomy, multiple intercostal neurectomy, that serve more exactly to fulfill certain varied indications for treatment. The necessity for a wide variety of operative procedures has been more pressing during recent years. The indications for treatment have become much more complicated since the general acceptance for collapse therapy of cases that only a few years ago were being rejected for this treatment because of extensive bilateral involvement or bilateral cavities.

Although it has not been possible to report treatment results of a control series in contrast to the final results in this group of 1124 patients, we have been unable to find in the literature any reports of cavity closure and sputum conversion in a comparable inclusive series of patients that in any way approach the excellent results reported here. These results have been summarized for all groups of discharged and resident surgical and non-surgical patients in Table 5.

McMahon and Kerper,² whose report is representative of other controlled published series, reported the results of cavity closure in 296 patients. The cavities closed with bed rest alone in 65 cases, or 22% of the series. In 62 patients collapse therapy was instituted within 2 months of admission, and cavities became closed in 43% of these; of the remaining 169 patients, collapse therapy was later resorted to in 83, and cavities were closed in 23, or 27.7% of these. Final cavity closure was secured in 115 cases, or 38.8% of the entire series.

These figures compare as follows with those in Table 5; total cavity closure, 38.8% (McMahon series), and 61.2% (Michigan State Sanatorium); closure of cavities for patients receiving surgery, 34%, as compared with 71.5% in our series. Inasmuch as in the McMahon and Kerper series, slightly less than 50% of patients received collapse therapy, and in 57% of these the collapse was delayed, these comparative figures present the strongest possible argument for the early and general application of collapse therapy, without the delay required to learn which patients might do well without such treatment. It is, of course, well known to observing phthisiologists that tuberculous lesions, in the presence of an open cavity, may at any time unexpectedly spread or otherwise become more difficult to treat successfully.

TABLE 5.—SUMMARIZATION OF RESULTS OF TREATMENT OF DISCHARGED, RESIDENT AND ENTIRE ADMISSION GROUP.

Cavity cases, 831.		Discharged patients, 823.						Resident patients, 301.						Combined, 1124.					
		Surgical 595		Non-surgical 228		Combined 823		Surgical 291		Non-surgical 10		Combined 301		Surgical 886		Non-surgical 238		Combined 1124	
		With cav-ities.	Per cent.	With cav-ities.	Per cent.	With cav-ities.	Per cent.	With cav-ities.	Per cent.	With cav-ities.	Per cent.	With cav-ities.	Per cent.	With cav-ities.	Per cent.	With cav-ities.	Per cent.	With cav-ities.	Per cent.
Cavities closed*	Minimal	2	100.0	2	100.0	2	100.0	3	100.0	1	100.0	3	100.0	5	100.0	3	27.3	5	100.0
	Mod. adv.	120	90.2	20	20.0	122	85.3	59	86.8	1	100.0	60	87.0	179	89.0	3	27.3	182	85.8
	Far adv.	204	63.4	6	5.0	210	47.6	112	65.5	112	64.7	316	64.1	6	5.0	322	52.4
Total		326	71.3	8	6.2	334	57.0	174	71.9	1	33.3	175	71.4	500	71.5	9	6.8	509	61.2
Cavities decreased	Minimal	5	3.8	1	10.0	6	4.2	6	8.8	6	8.7	11	5.5	1	9.1	12	5.7
	Mod. adv.	54	16.8	14	11.8	68	15.4	49	28.7	2	100.0	51	29.5	103	20.9	16	13.2	119	19.4
	Total	59	12.9	15	11.6	74	12.6	55	23.7	2	66.7	57	23.3	114	16.3	17	12.9	131	15.8
Cavities unchanged or increased	Minimal	..	6.0	7	70.0	15	10.5	3	4.4	3	4.3	11	5.5	7	63.6	18	8.5
	Mod. adv.	64	19.8	99	83.2	163	37.0	10	5.8	10	5.8	74	15.0	99	81.8	173	28.2
	Total	72	15.8	106	82.2	178	30.4	13	5.4	13	5.3	85	12.2	106	80.3	191	23.0
Total number patients with cavities	Minimal	2	of 39	2	of 51	2	of 90	3	of 13	1	of 2	3	of 15	5	of 52	1	of 53	5	of 105
	Mod. adv.	133	of 215	10	of 48	143	of 263	68	of 98	..	of 4	69	of 102	201	of 313	11	of 52	212	of 365
	Far adv.	322	of 341	119	of 139	441	of 470	171	of 180	2	of 4	173	of 184	493	of 521	121	of 133	614	of 654
Total		457	of 593	129	of 228	586	of 823	242	of 291	3	of 10	245	of 301	699	of 886	132	of 238	831	of 1124

1124 patients.			Discharged patients, 823.						Resident patients, 301.						Combined, 1124.					
			No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Sputum becoming negative*	Minimal	6	13.4		7.8	10	11.1	3	23.1	3	20.0	9	17.3	4	7.5	13	12.4
	Mod. adv.	113	52.6		12.5	119	45.3	49	50.0	49	48.1	162	51.8	6	11.6	168	46.0
	Far adv.	208	61.0		7.8	218	46.4	110	61.1	110	59.8	318	61.0	10	7.5	328	50.1
	Total	327	54.9		8.8	347	42.2	162	55.7	162	53.8	489	57.9	20	8.4	509	45.3
Sputum remaining negative	Minimal	33	84.6		90.2	79	87.8	10	76.9	2	100.0	12	12	80.0	43	82.7	48	90.6	91	80.7
	Mod. adv.	88	40.9		77.1	125	47.5	35	35.7	4	100.0	39	39	38.2	123	39.3	41	78.8	164	45.0
	Far adv.	24	7.1		5.4	31	6.6	15	8.3	1	25.0	16	16	8.7	39	7.5	8	6.0	47	7.2
	Total	145	24.4		39.5	235	28.5	60	20.6	7	70.0	67	67	22.3	205	23.1	97	40.8	302	26.9
Sputum remaining positive*	Minimal	11	6.5		2.0	1	1.1	..	14.3	14	13.7	28	8.9	1	1.9	1	0.9
	Mod. adv.	109	31.9		86.8	221	47.0	55	30.6	3	75.0	58	58	31.5	161	31.5	115	86.5	33	9.0
	Far adv.	123	20.7		51.7	241	29.3	69	23.7	3	30.0	72	72	23.9	192	21.7	121	50.8	279	42.7
	Total	243	43.1		139.5	462	57.4	124	48.3	6	60.0	134	134	47.1	381	43.6	237	93.2	414	36.6
Totals	Minimal	39	100.0		100.0	90	100.0	13	100.0	2	100.0	15	15	100.0	52	100.0	53	100.0	105	100.0
	Mod. adv.	215	100.0		100.0	263	100.0	98	100.0	4	100.0	102	102	100.0	313	100.0	52	100.0	365	100.0
	Far adv.	311	100.0		100.0	470	100.0	180	100.0	4	100.0	181	181	100.0	521	100.0	133	100.0	654	100.0
	Total	595	100.0		100.0	823	100.0	291	100.0	10	100.0	301	301	100.0	886	100.0	238	100.0	1124	100.0

* See notes at bottom of Table 2.

A further article is being prepared for early publication, which indicates the selection and distribution of nine different collapse therapy procedures, either singly or multiply in complementary sequence, according to the various indications, in this series of 1124 patients.

Summary. The final results of an intensive collapse therapy program are detailed for a series of 1124 patients of a single large sanatorium, including 823 discharged and 301 resident patients.

Collapse therapy in some form was instituted in 72.3% of the discharged patients. It was recommended in 81% of the entire series of 1124 patients, and was actually used in 78.8%.

Of 823 discharged patients, arrest or apparent arrest of the tuberculosis was secured in 47.3%; favorable results in 67.1%; cavity closure in 57% of cavity cases; closure or decrease in the size of cavities in 69.6%; sputum conversion in 59% of the positive cases; negative sputum in 70.7% of the discharged patients, of whom only 28.6% had negative sputum throughout the entire period of treatment.

Of 595 discharged patients who received collapse therapy, the figures for similar results were invariably much higher, being, respectively, 55.4, 77.8, 71.3, 84.2, 72.7 and 79.3%.

Corresponding figures for cavity and sputum results for the entire series of 1124 patients were usually slightly higher than the foregoing figures for the discharged group alone. Satisfactory explanations account for this apparent anomaly.

A comparison of the results of an intensive program of collapse therapy reported in this article, with those of a large number of sanatoria using relatively little collapse therapy as an average, clearly shows that the former are vastly superior from every point of view.

It is obvious that the results presented in this study constitute an overwhelming argument in favor of a definitive policy of early and intensive collapse therapy for approximately three-fourths of the patients with the adult type of tuberculosis in the civilian sanatoria of this country.

The authors wish to express their indebtedness to Dr. John Alexander for valuable critical advice in the preparation of this article.

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DIAGNOSIS OF DISEASES OF THE STOMACH BY GASTROSCOPY AND X-RAY RELIEF STUDIES.

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DURING the last two decades the emphasis in the clinical diagnosis of stomach diseases has shifted more and more from evaluation of the anamnesis and exploration of the functions to morphologic evidence of the condition of the stomach wall. This has increased considerably the number of correct diagnoses as proved by biopsy and necropsy. At present there are two non-surgical methods available which show anatomic changes: X-ray examination and gastroscopy. These are based on entirely different principles and they developed along entirely different lines. The basis for modern x-ray diagnosis was the development of a technique which attempted to demonstrate the changes of the mucosal relief in addition to the opaque shadow of the stomach as a whole. Whereas both methods are practised in many continental hospitals, particularly in Germany, there are only a few institutions in this country wherein both are routine procedures. Therefore it seems justifiable to present studies on even as few as 100 cases which were thoroughly examined by x-ray relief method and gastroscopy. An attempt was made by repeated checks to elicit in the individual case why the one or other method was superior or failed. Before discussing the details the essentials of both procedures may be briefly outlined.

Even during the early days of x-ray examination of the stomach Holzkecht⁹ and his co-workers realized that the mucosal folds could be visualized with fluoroscopy before the stomach was completely filled with the opaque substance. The use of a small amount of opaque medium was originally applied for various reasons by v. Elischer³ in 1911. For the demonstration of the folds of the mucosa it was first used by Forsell^{6a} (1913), while Rendich,¹⁷ in 1923, applied these experiences to clinical problems, and since many authors have contributed. The most outstanding work was by H. H. Berg² and his pupils. His book, "Roentgenuntersuchungen am Innenrelief des Verdauungskanaals," gives a complete review of recent developments in this field of diagnostic study.

The greater efficiency of modern x-ray visualization of the stomach is due to the application of four principles:

1. The use of a small amount of opaque medium in order to maintain some degree of transparency.
2. The application of graded compression in order to fill the depressions between the prominent structures of the mucous membrane.
3. Fluoroscopy of the patient in various positions demonstrating the contours of the stomach in different planes.

4. Small pictures snapped in selected positions during fluoroscopy enabling the examiner to obtain permanent records of fleeting observations.

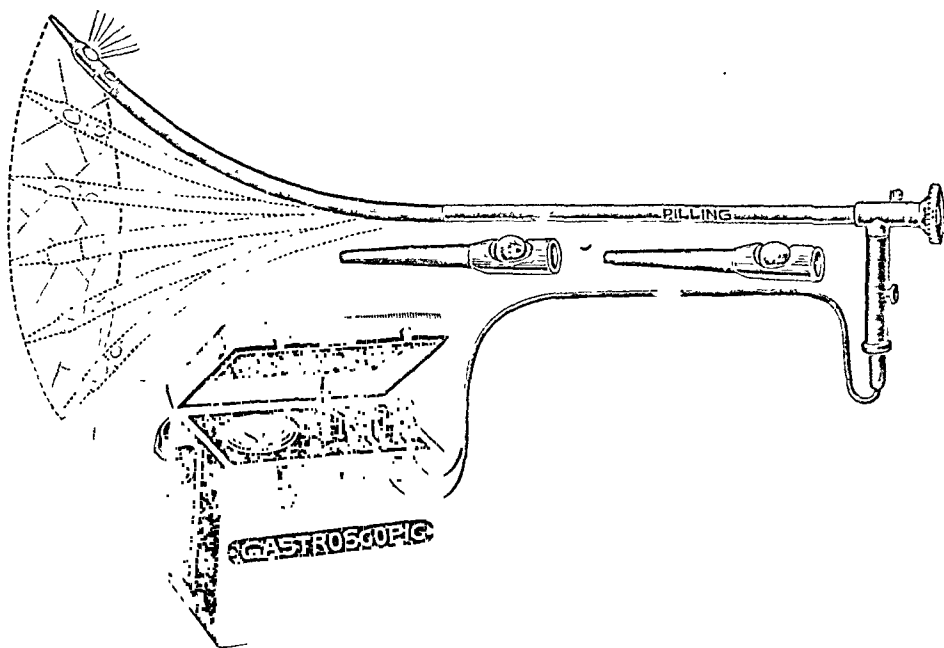
Gastrosocopy may be defined as the intravital inspection of the stomach mucosa by a non-operative procedure. In a strictly historical sense gastrosocopy is older than *x-ray* examination. As long ago as 1868, Kussmaul¹³ introduced a metal tube into the stomach of a sword swallower hoping to see the interior of the organ. His attempts were naturally failures because suitable sources of light were not available in the early years. The first report concerning successful gastrosocopies was published by von Mikulicz,¹⁵ in 1884. In the years following von Mikulicz' publication the attempts never ceased entirely and many instruments were devised which finally were abandoned for one reason or another. It was not until 1910 that more serious attempts at developing gastrosocopy as a method of research and finally of clinical diagnosis were made. Since 1910, several instruments have been devised which have been more efficient and less dangerous than their predecessors (Loening and Stieda, 1910;¹⁴ Elsner, 1911;^{4a} Schindler,^{18a} Korbsch^{12b} and others). All these instruments were of the rigid type and therefore restricted to application by only a few well-trained and particularly skillful examiners. However, we owe to this pioneer work with the rigid gastroscope most of the knowledge upon which the present-day routine gastrosocopy is based (Elsner,^{18d} Schindler,^{12d} Korbsch,^{12a} Gutzeit,⁷ Henning,^{8d} Moutier¹⁶ *et al.*). The device which finally paved the way for the more general use of gastrosocopy was the semi-flexible (or semirigid) gastroscope, constructed by Georg Wolf, of Berlin, in collaboration with Schindler.^{18c} From a technical viewpoint this instrument represents an entirely new principle. The rigid instruments were constructed like telescopes, *i. e.*, they contained a rather simple system of prisms and lenses. The Wolf-Schindler gastroscope consists of a rigid upper portion and a semi-rigid lower end. This lower end is constructed with overlapping rings after the fashion of the fish-scale arrangement of medieval armor. The optical arrangement of the rigid part is similar to that in the original instruments. The lower part contains a complicated system of lenses with short focal distances. The main advantages of the Wolf-Schindler gastroscope are that its application certainly demands much less training than the use of the rigid tube and the danger of perforating the esophagus or the stomach is considerably lessened.

There has been, and still is, much controversy as to the advantages and disadvantages of flexible instruments. We regard Chevalier Jackson's¹⁰ criticism as important. As the Wolf-Schindler gastroscope is equipped with a 90-degree optic, or after the suggested modification of Henning^{8c} with a retrograde optic, the instrument must necessarily be passed through the esophagus blindly. It is obvious that an unexpected obstruction in the esophagus or the cardia may lead to perforation. For this reason, we require careful *x-ray* studies of the esophagus, or better, esophagoscopy to precede

the introduction of the gastroscope in cases in which there is any possibility of such a complication.

We have recently used a telescopic esophagoscope as devised by Wolf and Henning.^{8b} This instrument causes scarcely any discomfort to the patient because its diameter is only 7.3 mm. It is equipped with two exchangeable telescopes, one of which represents a prograde system. This permits fulfillment of Jackson's demand that one "see the esophageal lumen ahead."

The actual examination is usually carried out with the patient lying on the left side. The optimum time for the examination, as with x-ray studies, is in the morning, the patient having fasted over night. One hour before gastroscopy we ordinarily administer a



New type of flexible gastroscope after Wolf-Schindler, with rigid upper part with eyepiece, electric wiring and mouth of air channel; and flexible lower part with the window, illuminating bulb and rubber tip. (Illustration furnished by The George P. Pilling & Son Co., Philadelphia.)

sedative, the type and amount depending primarily on the emotional state of the patient. Immediately before the examination a local anesthetic is applied to the mouth and pharynx, and a gastric lavage with a large rubber tube is performed. The latter procedure serves to demonstrate whether difficulties in the introduction of the gastroscope may be expected and permits removal of stomach contents which may hamper the inspection of the gastric wall.

Summarizing the principles of both methods, we may say that the x-ray examination is a study of an elaborate plastic cast of the entire organ; gastroscopy gives an immediate natural picture of circumscribed areas of the interior surface of the stomach which can be pieced together like a mosaic pattern. From such considerations we may possibly predict what types of lesions would be revealed best by the former or the latter procedure.

X-ray examinations may inform us about shape, size, contour, tone, motility, peristalsis and position of the stomach. They may

give some information about emptying time and gastric secretion. They may show large and medium-sized defects of the walls and, with the application of modern principles of relief technique, may also reveal comparatively coarse changes of the mucosa itself and of the mucosal folds.

Gastroscopy, on the other hand, may demonstrate even very fine changes and defects of the surface; it shows the folds in their natural appearance. It demonstrates the color of the mucous membrane, the distribution of blood, the filling of the blood-vessels, hemorrhages and so on. It may also give some impression as to tone, peristalsis and gastric secretion.

We may, therefore, expect that the x-ray examination is superior where localized lesions, especially if not too small, are present; whereas generalized pathologic processes and very fine superficial changes are more the domain of the gastroscope. Therefore, the two methods are in no way in competition, but supplement each other successfully. The very lesions which x-ray examination fails to reveal can usually be visualized with the gastroscope, while those which can scarcely be seen by gastroscopy seldom cause difficulties for the roentgenologist.

The following table summarizes and compares 100 consecutive cases in which both methods were used; in cases where there was disagreement in diagnosis an attempt has been made to explain the reason therefore. In many instances repeated examinations were necessary before a satisfactory explanation was reached.

TABLE 1.—ANALYSES OF 100 CONSECUTIVE CASES IN WHICH BOTH "RELIEF" RADIOLOGIC EXAMINATION OF THE STOMACH AND A DIRECT INSPECTION OF THE GASTRIC MUCOSA WITH A GASTROSCOPE WERE MADE.*

		Clinical diagnosis.	X-ray diagnosis.	Gastro- scopic diagnosis.
I. Normal stomach and functional disturbance	Normal	2	25	16
	Gastric neurosis	17		
	Undiagnosed	2		
	Cyclic vomiting	1		
	Diverticulum of esophagus	1		
II. Extragastric lesions	Carcinoma of esophagus	1		
	Cholecystitis	1		
	Cancer metastasis, extragastric		1?	
	Gastritis (various forms)	12	21	32
	Erosive gastritis			7
III. Chronic gastritis	Atrophy		4	4
	Hyperchromic anemia	2		
	Hypochromic anemia	5		
	Multiple hemorrhages			1
	Peptic ulcer	34		
IV. Ulcer	Gastric ulcer		11	18
	Duodenal ulcer		13	
	Duodenal scar		3	
V. Tumors	Polyp		1	2
	Carcinoma	14	13	12
VI. Postoperative conditions		8	8	8

* In every case in the column headed "clinical diagnosis" the tentative diagnosis is recorded. This was made before the special procedures were undertaken which accounts for the discrepancies in the 3 columns. For detailed analysis see the following text.

At first sight one may get the impression from Table 1 that there is at least in a few groups fair conformity between clinical, roent-

genologic and gastroscopic diagnosis. On the other hand, further analysis shows that in such a small series of cases the fairly close agreement of the three methods is in some instances only apparent, and *vice versa*. It is probable that most errors may be expected on the side of the clinical diagnoses. Therefore, most of these figures require a short explanation and many a rather detailed discussion.

If we exclude in Group I the 2 cases where with a mere clinical examination no diagnosis could be made and the 1 case of frequent probably vicarious hematemesis, there are left 19 cases in which no organic lesion could be expected from the clinical findings. This is slightly below the number of normal cases obtained by x-ray¹⁴ namely 25, and slightly above the number of cases^{8a} which showed no changes in gastroscopy. Further analysis revealed the fact that the clinical studies were even less dependable.

In these 19 cases where the clinical diagnosis was normal or gastric neurosis, the following findings were obtained:

	X-ray examination.	Gastroscopy.
Normal	12	7*
Gastritis	5	8
Gastric ulcer	0	3
Carcinoma	1	1
Atrophy	1	0

* Including 1 case of *état-mamelonné* and 2 cases of anemia.

The difficulty in x-ray diagnosis of atrophy will be discussed later. Thus further analysis of 19 cases without suggestive clinical symptoms or signs showed that in about two-thirds significant anatomic changes could be demonstrated. Two-thirds of the "normal cases" certainly deserved other treatment than psychotherapy and could be treated at an earlier time, *i. e.*, before complications occurred, when proper treatment still promised to be successful.

Group II includes cases where stomach lesions were found more or less incidentally. Naturally the clinical diagnosis in these 3 cases were failures. One case which actually belongs in this group may be mentioned because it shows the advantage of close collaboration of x-ray and gastroscopy. In this case the x-ray examination showed a large defect probably due to carcinoma. It was not possible to decide by x-ray examination alone whether this mass, which was firmly attached to the stomach, was extrinsic or intrinsic. Gastroscopic examination proved that the lesion did not involve the stomach itself. Therefore, intra-abdominal metastases were assumed and finally the primary tumor could be demonstrated in the colon. The therapeutic approach to this case certainly was entirely different after these facts were established.

Group III summarizes all cases where gastritis was the main diagnosis. It was through the close coöperation of surgeon, roentgenologist and gastroscopist that the diagnosis of gastritis which has been in disrepute during a few decades has again received an anatomic basis. In the recent American literature gastritis does not find as prominent a place as in the European. The opinion was even brought forward that this condition, frequent in central Europe,

is extremely rare in central North America (Walters and Sebening,¹⁹ Eustermann and Balfour).⁵ We felt that the more general use of both α -ray relief technique and gastroscopy in Europe is responsible for this discrepancy. In 1935, Benedict¹ has already reported that in the Massachusetts General Hospital, where both methods are used routinely, in 40 out of 200 cases chronic gastritis was diagnosed.

The roentgenologic diagnosis of gastritis is usually based upon indirect signs such as hypersecretion, hyperperistalsis, broadening and increased rigidity of the rugæ. Only in rare instances does the α -ray examination succeed in the demonstration of the so-called "granulated relief." These "granula" are direct signs of hypertrophy, and correspond to the "wart-like" swellings of the mucosa so often encountered in gastroscopy.

A great variety of findings in gastroscopy corresponds to these comparatively uniform α -ray pictures. Among the direct signs of gastritis representing changes of the epithelium itself may be mentioned spongy velvet-like appearance of the surface, edema, circumscribed hyperemia, old and fresh hemorrhages, verrucous swellings probably preformed by the normal grouping of the stomach epithelium into alveoli, erosions, atrophic areas and so on.

It is superfluous to mention that the "indirect" signs of the α -ray examination, namely, hypersecretion, hyperperistalsis, broadening and increased rigidity of the folds are also seen with the endoscope.

The most impressive α -ray sign of "hypertrophic" gastritis is, as mentioned, the enlarged fold. Gastroscopic studies proved, however, that the thickened fold frequently, but not always, accompanies the hypertrophic changes of the mucosa. It seems most likely from recent investigation of the subject that the enlargement of the fold is due to functional changes of the submucosa and muscularis mucosæ rather than to true gastritic processes (Forsell,^{6b} Henning^{3d}). In other words, the most impressive α -ray sign is only a frequent but not a constant finding in hypertrophic gastritis.

The roentgenologist often believes that the thickening of the folds allows the diagnosis of hypertrophic gastritis to be made. We agree with Henning^{3d} that this "hypertrophic gastritis of the roentgenologist" does not necessarily represent true hypertrophic changes of the mucosa. We may find enlargement of the folds in the normal stomach and sometimes even in complete atrophy. This series of 100 cases includes 1 in which α -ray examination recorded broadening of the relief while gastroscopy demonstrated all the signs of complete atrophy.

The great variety of anatomic changes as seen through the tube induced Schindler^{18b} to subdivide the anatomic picture of chronic gastritis into three groups: Superficial, hypertrophic and atrophic gastritis. This classification is still used, although there is general agreement among gastroscopists that it is highly unsatisfactory. Actually we very often find features of different groups of Schindler's classification in the same case of chronic gastritis. Therefore, Henning^{3a} prefers to express this fact in the gastroscopic diagnosis. He attempts to express in the diagnoses all

the significant findings. Following his suggestion one would speak, for example, of gastritis with predominance of atrophic processes and so on. We do not intend to enter into this discussion. Therefore, we classify in our statistics most of the cases of gastritis under the heading "chronic gastritis (various forms)."

We feel, however, that two types should be discussed separately, *i. e.*, the gastritis with multiple erosions and the complete atrophy without any demonstrable signs of chronic inflammation. The former deserves special attention because we can observe good agreement between the presence or even the stage of the erosions and the symptoms of the patients. We saw repeatedly that pain and other symptoms disappeared at the same time that the erosions healed. The *x*-ray films at this stage may and usually do show the same picture of "hypertrophic gastritis" as at the beginning of the treatment. Therefore, we make it a rule to keep the patient on a strict diet until the erosions are gone, although we attempt to continue the treatment in a milder form until the other signs of gastritis disappear or are considerably lessened. Unfortunately, the conformity between the complaints of the patient and the gastroscopic picture is less dependable in other manifestations of chronic gastritis. We see very often severe gastritic changes in cases with only minor symptoms and *vice versa*. As in other conditions of the stomach so also in gastritis, the constitution, psyche and personality of the patient seem to play an important part in the subjective reaction of the patient to the disease.

The signs of localized atrophic changes are often met together with other signs of chronic inflammation. If they occupy large areas of the stomach we may safely speak of chronic gastritis with predominance of atrophic changes or, in a word, atrophic gastritis. On the other hand, we prefer to classify as atrophy, cases where we find complete atrophy without signs of chronic inflammation as frequently in cases of pernicious anemia. This leaves the question open as to whether these lesions are of inflammatory or degenerative origin. We used to think of atrophy in pernicious anemia as a final condition with no tendency to recovery. Recently, Jones, Benedict and Hampton¹¹ believed that they could prove that following successful treatment the signs of atrophy may disappear.

We agree with Berg that the thin fold in *x*-ray examination certainly justifies the diagnosis of atrophy only in rare instances. We feel that the *x*-ray diagnosis of atrophy is more or less guesswork. The following two tables may prove this statement.

GASTROSCOPIC DIAGNOSIS IN 4 CASES DIAGNOSED AS "ATROPHY" BY X-RAY.

Hypertrophic gastritis (in stomach with gastro-enterostomy)	1
Normal mucosa	1
Hemorrhages in otherwise normal stomach	1
Atrophy	1

X-RAY DIAGNOSIS IN 4 CASES WHERE ATROPHY WAS SEEN THROUGH THE GASTROSCOPE.

Normal mucosa	3
Atrophy	1

It also seems of interest to review the diagnoses which were made in the 38 cases where gastritis was the only diagnosis revealed with the gastroscope. The following table includes the 31 cases of various forms of chronic gastritis and the 7 cases of erosive gastritis. The following are the clinical diagnoses of these 38 cases:

Peptic ulcer	17*
Gastritis	10
Neurosis	8
Carcinoma	2
Not diagnosed	2

* Including 8 cases where the *x*-ray examination proved the presence of a duodenal ulcer.

Finally we want to emphasize that Table 1 contains in the columns "*x*-ray examination" and "gastroscopy" cases in which gastritis was the only diagnosis. Most of the stomach and duodenal lesions such as ulcerations or cancer are also accompanied by gastritic changes. If we include these the frequency of the diagnosis of gastritis rises considerably. The total number of cases in which marked gastritic changes were observed (with or without other pathologic changes) was:

On <i>x</i> -ray examination	40 cases out of 100
On gastroscopy	62 cases out of 100

In any event we must realize that many cases of gastritis cannot be diagnosed by the *x*-ray method. This proves, what we expected *a priori*, that generalized lesions of the stomach are more easily diagnosed with the gastroscope.

In a similar way we see the verification of our prediction that probably small defects may be overlooked in *x*-ray. Of the 18 gastric ulcers seen with the gastroscope only 11 were demonstrable in *x*-ray examination (Group IV of Table 1). We want to stress the point that we classify under the heading of ulcer only deep lesions whereas superficial lesions in these statistics are regarded as erosions. Gutzeit⁷ reports a similar experience. He found in 100 cases of gastric ulcer that the diagnosis was possible in 45 cases by *x*-ray and in 75 cases by gastroscopy. This, however, is practically the same proportion which we observed on a smaller scale. Another advantage of gastroscopy is that complete healing of an ulcer can be shown with certainty. It happens quite frequently that on gastroscopic examination the ulcer is still present, although the *x*-ray signs have already disappeared.

Although the duodenum is not within the reach of the gastroscope, it may be of interest to record the gastroscopic findings in 16 cases where the *x*-ray examination revealed pathologic changes in the duodenum. In 13 cases of active duodenal ulcer evidenced by *x*-ray the gastroscopic findings were:

Severe gastritis	8
Mild gastritis	4
Deformed pylorus	1

In 3 cases of inactive duodenal ulcer:

Severe gastritis (with deformity of the pylorus)	1
Normal (<i>i. e.</i> , no pathological changes in the stomach except for deformity of the pylorus)	1
Gastric ulcer (not found in x-ray)	1

As to the diagnosis of carcinoma of the stomach, there is in our series satisfactory agreement between x-ray examination and gastroscopy. In 1 case the x-ray examination carried out at another hospital and repeated by us suggested malignancy of the greater curvature. Gastroscopic examination revealed localized inflammatory changes in the area where the lesion had been visualized by x-ray. The gastroscopist was opposed to surgical intervention. This patient gained more than 25 pounds during the following year and is at present free from pain or other symptoms.

The efficacy of both methods in our cases may be largely due to the fact that all of our patients showed major lesions when they first came for examination. From previous experience and other publications we got the impression that a small carcinoma might be more easily overlooked with the gastroscope, than with x-ray relief technique. As far as we know, Schindler^{18c} alone feels that gastroscopy is the superior method in the diagnosis of very small stomach tumors. On the other hand, we feel that while these tumors are frequently discovered on x-ray examination, gastroscopy is very helpful in establishing their nature and extent. Sometimes it may happen that small tumors are discovered by gastroscopy before they can be demonstrated by x-ray. Table 1 shows 1 case of a solitary polyp which could be diagnosed only through the endoscope. The advanced stage of the disease when our patients first came under observation is shown by the fact that in 8 of the 12 cases of cancer the diagnosis was already suggested by the clinical signs and symptoms. In the remaining 4 cases the clinical diagnoses were respectively pernicious anemia, gastritis in an operated stomach, peptic ulcer and neurosis.

Late changes of the postoperative stomach are often very impressive in x-ray examination and even more so in gastroscopy. It is rare to find a stomach after operation of any type that does not show severe gastritis changes. As a rule, lesions on the stomach side of an anastomosis are disclosed more readily on direct inspection with the gastroscope; lesions of the anastomosed viscus when opposite to the opening may also be seen with the tube. Lesions of the intestines proximal and distal to the stoma may be seen only by x-ray.

Of the 8 cases of postoperative stomach in our series in 1 a carcinoma could be demonstrated by x-ray and gastroscopy. In 1 case complete atrophy and in another a chronic gastritis with predominantly atrophic changes were seen with the tube. The x-ray reports were hypertrophic gastritis and normal stomach mucosa, respec-

tively. In 2 cases severe gastritis and jejunitis were diagnosed by both methods. On one occasion a jejunal ulcer discovered by x-ray could not be seen through the gastroscope, and in 2 instances ulcers at the gastro-enterostomy opening could be found by gastroscopy only.

Summary and Conclusions. 1. Both x-ray relief technique and gastroscopy represent a decided improvement over the previous routine in the diagnosis of stomach diseases.

2. The combined use of both methods as a routine procedure is an additional help in diagnosis and in the investigation of unsolved problems in the pathology of the stomach.

3. One hundred cases in which careful and sometimes repeated examinations with both methods have been carried out are subjected to analysis and compared with the results of clinical examination.

4. For the diagnosis of gastritis, gastroscopy is by far superior to x-ray relief technique. Erosions and atrophy of the stomach mucosa can be diagnosed for all practical purposes by gastroscopy only.

5. Gastric ulcers are more frequently encountered in gastroscopy than in x-ray. In cases of duodenal ulcers almost always accompanying changes in the stomach are present.

6. For the diagnosis of stomach tumors and of postoperative changes, x-ray relief method and gastroscopy supplement one another in an almost ideal way.

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THE BONE MARROW IN ANEMIA.***THE RED BLOOD CELLS.**

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WITH the advent of the liver and stomach therapy of pernicious anemia and the revival of the method of treatment of "secondary" anemia with massive doses of iron, the necessity for a critical analysis of the indication of these types of treatment has become more evident. Ultimately, it is the state of the cells in the bone marrow that determines the reactivity of the patient to a given type of therapy. Many terms are used to describe the state of the bone marrow: it is said to be hyperplastic, hypoplastic, aplastic, depleted, stimulated, depressed, exhausted, irritated, injured, recovered, normoblastic, megaloblastic or myelophthisic. It would be more desirable to substitute a more exact description in terms of numbers of cells per cubic millimeter, and relative percentages of the different kinds and stages.

A number of studies of the sternal marrow have appeared recently in the literature. Those of Custer,¹ Fitz-Hugh and Krumbhaar,³ Krumbhaar and Custer,⁵ and Dameshek² deal with studies of sections of bone marrow and are not strictly comparable to the work reported here. Reich⁶ and Young and Osgood⁷ used films of bone marrow made from material obtained by aspiration of blood and bone marrow cells. This method gives very good cytological preparations, but is not quantitative and represents only those cells which are most easily dislodged. The touch or imprint method, while giving the best cytological pictures, does not give a true distribution of all types of cells, many of them not being represented in the film. The sections are indispensable for determining the architecture and arrangement of the bone marrow, as well as the determination of the relative distribution of fat and cellular tissue. However, it is often difficult, because of different technical treatment, to name the bone marrow cells in the same terminology as those which appear in the peripheral blood. For this reason the special technique used in this study helps to correlate the quantitative and qualitative relationships between the cells of the marrow and those of the peripheral blood.

In these studies the descriptions are limited to the condition in the sternal bone marrow, although data have been accumulated on the marrow of the femur, tibia, vertebrae and ribs. The sternal

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marrow has the advantage of accessibility, as well as being a relatively stable source of both red and white blood cell forming tissue.

The principle of the technique depends upon the fact that blood serum dissolves intercellular connective tissue substance, liberating the individual cells, and changing them chemically so that they stain like cells of the blood stream.⁴² The technique is as follows:

Method for Counting Cells of the Bone Marrow.⁴³ Wet the inside of the tube of a Sahli hemoglobin pipette, or the stem of a red or white blood cell counting pipette with serum. The pipette stem should have markings enabling one to measure 4 volumes. A serum of the same blood group as the patient is desirable if the red blood cell count is a factor, otherwise any blood serum may be used. The serum is drained out, and bone marrow is sucked up 1 unit of space into the pipette. By working the tip back and forth among the trabeculae of bone, enough marrow may be obtained without air bubbles. Serum is then drawn up so that the total bulk is 4 volumes. This is then discharged into a watch glass, using care to wash out all of the marrow. Eight more volumes of serum (measured by the markings on the pipette) are then added, and the suspension is stirred thoroughly with a blunt glass rod. This suspension is then drawn into a red blood cell counting pipette to the 0.5 mark, and diluted with Hayem's solution, or with 1% acetic acid, the rest of the steps being exactly as in the case of counting red blood cells, using a hemocytometer slide. The high-dry objective is used. The total number of cells in 4 or 8 sq.mm. are counted, the adult red blood cells being enumerated in one group (if acetic acid has not been used) so that when their number is subtracted from the total, the number of nucleated cells of all types is obtained. The calculations are as follows:

The number of cells counted in 1 sq.mm., obtained by dividing the total number of cells counted by the number of square millimeter spaces used, is multiplied by 24,000, *i. e.*,
$$\frac{10 \times 12 \times 200}{\text{No. of sq.mm.}}$$

The differential count is made from cover glass films, using a thick emulsion of bone marrow in serum. The fresher the serum, the better are the results. If the serum is of the same blood group, the red blood cells show a better distribution than when they are agglutinated. Human serum may be used for bone marrow of animals. Use Wright's or Giemsa's stain. When Wright's stain is used, allow the stain to act for 1 minute, then dilute with as much distilled water as the cover glass will hold, mixing very thoroughly. Allow this to stand for 10 minutes, then wash with distilled water, dry and mount in xylol-balsam.

The most "representative" bone marrow is obtained from the midsternum, as this gives both red and white cells in the course of their development. This technique may be used with marrow from any bone or for cells of other organs.

With careful technique, the variation in counting cells from the same region in the normal marrow, using several pipettes averages about 5%, an amount but slightly greater than variations from drop to drop in the same pipette. In pathologic marrows, where there was a grossly uneven distribution of the cells, the variation was considerably greater, amounting to as much as 24% between a cellular and relatively non-cellular region, and to 85% in marrows with regions of "aplasia."

MATERIAL. Bone marrow was taken from the midsternum of 163 patients at autopsy, including some observations on biopsy material. The biopsy material is, of course, more desirable for the finer cell structure. There are several other points of difference in the cells of the two types of

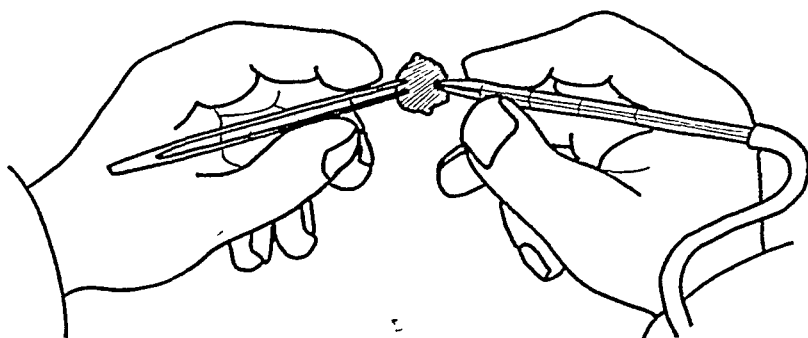


FIG. 1.—Method of drawing bone marrow, from fragment of marrow tissue removed at biopsy or autopsy, into pipette for measuring a unit volume.

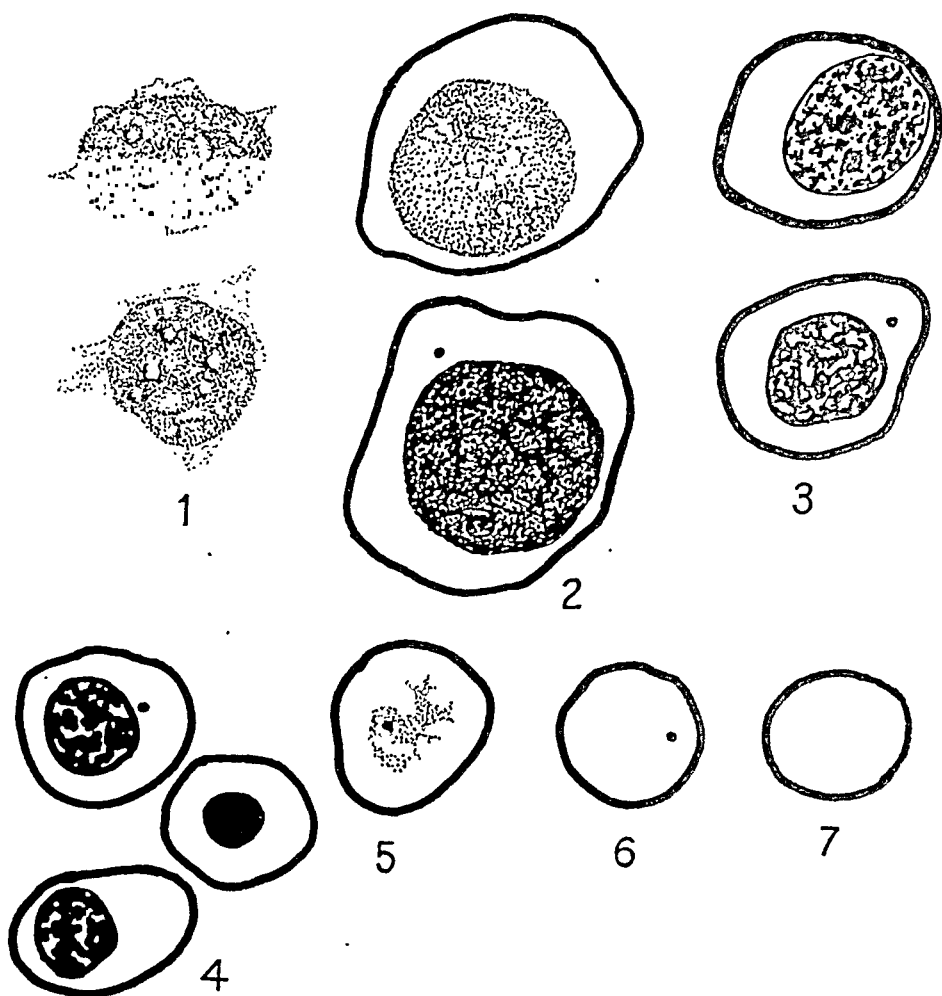


FIG. 2.—Stages in the development of red blood cells in the bone marrow of the sternum. (Camera lucida drawings, 10 ocular: 1.8 mm. oil-immersion objective; table level.) 1, Primitive blasts. It is possible that the oval nucleus type may represent a different cell (*c. g.*, precursor of the polymorphonuclear series or of the erythrocyte series) from the round nucleus form. 2, Megaloblasts. 3, Basophilic normoblasts. 4, Eosinophilic normoblasts. 5, Reticulocyte. 6, Granule red blood cell. 7, Mature erythrocyte.

material. The longer the period after death that the marrow is allowed to change, before films are made, the fewer the number of adult polymorphonuclear neutrophils, myeloblasts and myelocytes, although the change is not very marked. There does not appear to be a very extensive change in number of red blood cells in the various stages. In the cases selected the condition of the peripheral blood was studied before death, and also on the day of death or biopsy. From this group the following selections illustrate the characteristic features of each type of anemia.

Factors in the Interpretation of the Number of Cells per Cubic Millimeter in the Sternal Bone Marrow. In the non-diseased sternal bone marrow, the number of cells in each stage depends on the physiologic condition of the person at the time that the specimen is taken. There is less tendency for the marrow from different parts of the bone to vary in constitution in health than when a disease is present. There may be a variation in the predominant stage of development of the cells in the marrow of two different bones of the same patient in disease. Thus the sternal marrow in a patient with pernicious anemia in beginning remission showed the predominant stage of the red blood cells to be that of the eosinophilic normoblast, while the vertebral marrow showed most of the cells in the basophilic normoblast (macro-normoblast) stage. In a patient in complete remission, the red blood cells in both bones showed a predominance of the eosinophilic normoblast stage.

The "number of cells per cubic millimeter" represents the soft tissue. The amount of bony trabeculae varies in different individuals, so that the number of cells per cubic millimeter does not necessarily reflect the amount of marrow in the patient. In some patients there is a myeloid metaplasia in the spleen and other organs, and the extent to which the marrow spaces in such bones as the tibia and femur is utilized must be taken into account in considering the total amount of hematopoietically functioning marrow.

Cytologic Characteristics of the Cells of the Erythrocyte Series. The term "primitive blast" is used for a type of cell found in the bone marrow, but which appears in variable numbers in the peripheral blood in the terminal stages of chronic leukemias. In normal sternal bone marrow the average number varies from 150,000 to 300,000 per c.mm. The cells, in stained films of serum suspensions, have nuclei measuring 7.5 by 10 microns in diameter. The chromatin becomes finely reticular in the dried films stained with Giemsa or Wright, with no distinct nuclear membrane. There are 1 to 4 nucleoli. The cytoplasm, which is deeply basophilic, varies from a few shreds in the youngest stages to a thin ring around the nucleus in the older stages. The shreds may be fine filaments when no fluid is added to the films, but these, being jelly-like, may round up in fluids (as blood plasma or serum), and appear as "buds" of different sizes on the periphery. The cells enlarge as they grow, their cytoplasm becomes more distinctly marked off, and the typical myeloblast is produced. The "primitive blast" stage of the cells

of the polymorphonuclear leukocyte series resembles that of the lymphocyte and erythrocyte series of cells in general morphology, and may or may not be identical.^{4c}

The next stage in the development of the red blood cell is the *megaloblast*. We have found this type of cell in all specimens of normal bone marrow which we have examined and we take the point of view that it is a normal stage in the production of the erythrocyte rather than a pathologic or fetal cell. The average diameter in films from serum suspensions is 16 to 19 microns, and the nucleus is round and measures 12 microns. The chromatin is finely reticular and 3 to 4 nucleoli are visible. There is no sharp nuclear membrane. The cytoplasm stains a deep ultramarine blue with Wright's or Giemsa, and is hyaline. Individual cells show some spottiness of the cytoplasm with "moth-eaten" appearance of scattered areas. Under ideal conditions a single brilliantly refractile granule, 0.5 micron in diameter, taking no stain, but appearing black when in focus, is seen in the cytoplasm.

The next stage in development, the *basophilic normoblast* or macro-normoblast, is characterized by shrinkage in size and less intense basophilia of the cytoplasm. The chromatin network of the nucleus becomes more coarse, so that irregular lumps of chromatin material appear in the network. There is enough chromatin around the edge to suggest a nuclear membrane. The "moth-eaten" appearance of the cytoplasm becomes more marked, and an element of redness shines through the blue in these areas. In the fresh condition, and in certain of the stained cells which happen to be in the proper position, a brilliant refractile granule is visible in the cytoplasm. The nucleoli are not clearly evident, but in mashed cells they are definitely visible. In the films the nucleus measures 9 to 7.5 microns and the cytoplasm 15 to 12 microns in diameter.

The cells become progressively smaller, the nucleus more compact and the cytoplasm more eosinophilic. The *eosinophilic normoblasts* vary in size from 12 to 10.5 microns with nuclei from 6.75 to 5.75 microns in diameter. In some stained forms and in the fresh cells the refractile granule is visible in the cytoplasm. In some eosinophilic normoblasts nuclear particles are visible. They vary in number from 1 to 24. While they are usually regarded as fragmentation products of a decomposing nucleus, we think them to be chromosomes left out during the reconstitution of the nucleus following the last mitosis.

Three stages may be differentiated after this: the reticulocyte; the stage with only the brilliant refractile granule as a morphologic differentiation^{4d}; and the mature erythrocyte.

Sternal Marrow in the "Normal Individual." The bone marrow in "normal" individuals varies within wide physiologic limits as the preponderant type stage of development apparently differs

with different conditions of the body. A normal individual may tax his granulopoietic tissue at one time more than another in trying to remain normal. There is apparently a physiologic leukocytosis associated with certain phases of digestion, which may be expected to be associated with different rates of production. Thus the relative percentages differ considerably, making it difficult to evaluate a given specimen of a pathologic marrow by direct comparison, unless the variation is extreme.

In the bone marrow taken from the midsternum of 11 normal adults, or those dying from trauma (skull fracture, automobile accident; death following operation) the average cell distribution was as follows:

Total number of all nucleated cells per c.mm., 900,000 to 1,000,000.

	Per cent of all nucleated cells.
Undifferentiated "lymphoid" cells. "Primitive blasts"	23.1 \pm 8.0
Megaloblasts	3.0 \pm 1.0
Basophilic normoblasts	7.2 \pm 2.5
Eosinophilic normoblasts	12.0 \pm 7.0
<hr/>	
Polymorphonuclear neutrophils—adult	7.5 \pm 5.5
Polymorphonuclear neutrophils—young	13.0 \pm 6.0
Metamyelocytes	20.8 \pm 3.0
Myelocytes	2.8 \pm 1.8
Myeloblasts	1.8 \pm 0.8
Eosinophils (immature and mature)	5.5 \pm 3.0
Lymphocytes	1.0 \pm 0.5
"Endothelial" cells. Phagocytes	0.9 \pm 0.5
Hemohistioblasts and hemohistiocytes	2.3 \pm 1.3
Megakaryocytes	0.5 \pm 0.1
Basophils	Present
Monocytes	Present

"Aplastic" Anemia. In aplastic or hypoplastic anemia the total number of cells per cubic millimeter is greatly reduced and the fat content is increased. The "block" or stage of inhibition is in the "primitive blast" group, so that but few cells mature beyond this form. The so-called idiopathic aplastic anemia (6 cases) differs from the aplastic anemia following intensive Roentgen ray therapy (7 cases) in that in the latter condition the number of primitive blasts is reduced, but the cells which are present tend to ripen into eosinophilic normoblasts and later into mature erythrocytes. In the hypoplastic anemia of nephritis (10 cases) the inhibition is just after the primitive blast stage, so that cells in this stage accumulate in normal or greater than normal numbers while but few ripen to the megaloblast stage (Cases 1, 2, 3, Table 1).

Pernicious Anemia (16 Cases). In pernicious anemia in relapse, the point of inhibition appears at the megaloblast stage. Different individuals vary considerably in the degree of inhibition, correlated with the height of peripheral red blood cell count. In some individuals but few cells ripen, whereas in others a red blood cell count

TABLE 1.—HEMATOLOGIC DATA IN ILLUSTRATIVE CASES OF VARIOUS ANEMIAS.

Case No.	Condition.	Blood.			Bone marrow.							
		R.B.C. mill. per c.mm.	W.B.C. thous. per c.mm.	Hemo-globin, gm. %.	Total No. nucleated cells per c.mm.	Prim. blasts* per c.mm.	Prim. blasts, %.	Poly. series, %.	R.B.C. series, %.	Megalo-blasts, %.	Baso. nor-mobl., %.	Eosino. nobl., %.
1 . .	Aplastic anemia	1.00	4.8	2.10	216,000	76,600	35.0	52.5	0.7	0.1	0.4	0.2
2 . .	Hodgkin's Roentgen ray	1.20	18.0	2.80	192,000	22,800	12.0	61.0	15.0	1.0	0.5	13.5
3 . .	Chronic nephritis	1.32	12.0	2.52	660,000	349,800	53.0	28.0	18.0	1.0	10.0	7.0
4 . .	Pernicious anemia	1.67	13.0	6.72	1,440,000	336,900	23.4	46.2	11.1	7.0	3.0	1.1
5 . .	Cirrhosis of liver	1.91	4.9	5.04	1,448,000	434,000	30.0	22.5	24.9	11.5	6.7	6.7
6 . .	Cirrhosis of liver	2.90	4.1	5.04	882,000	506,000	57.5	20.0	13.0	4.0	6.0	3.0
7 . .	Acute hemorrhage	2.23	11.0	6.16	222,000	32,190	14.5	62.5	14.5	2.5	6.5	5.5
8 . .	Hemolytic anemia	1.54	7.6	4.06	840,000	494,800	47.0	17.0	33.0	4.0	7.0	22.0
9 . .	Myeloblastic leukemia	3.06	191.4	6.44	588,000	401,000	68.2	8.0†	21.0	3.5	14.5	3.0
10 . .	Chronic myelogenous leukemia	2.80	175.0	9.66	800,000	348,000	43.5	47.0	2.5	0.5	1.5	0.5
11 . .	Chronic lymphatic leukemia	1.97	52.0	4.76	1,380,000	1,276,000†	92.5	2.0	4.0	0.75	2.5	0.75
12 . .	Bronchopneumonia	4.50	32.4	9.10	720,000	100,800	14.0	50.0	17.0	3.0	11.0	3.0
13 . .	Gas bacillus infection	2.85	28.2	6.44	1,240,000	290,000	23.5	31.0	11.5	3.0	7.5	1.0
14 . .	Pneumonia	3.80	8.9	8.82	552,000	99,300	18.0	41.0	20.5	1.5	11.5	7.5
15 . .	Influenzal pneumonia; beginning empyema	3.50	8.0	8.40	906,000	312,600	34.5	36.0	18.0	1.5	15.5	1.0

* Both erythroblasts and leukoblasts. † More mature than the primitive blast stage. ‡ Including lymphoid cells.

* Both erythroblasts and leukoblasts.

† More mature than the primitive blast stage.

‡ Including lymphoid cells.

of 3 or more million may be maintained. Some patients with pernicious anemia showed a great increase in the actual amount of cellular tissue in the marrow (1,600,000 nucleated cells per c.mm.) whereas others showed a markedly hypoplastic condition (*e. g.*, 400,000 nucleated cells per c.mm.), although in both the "block" at the megaloblast stage was present (Case 4, Table 1).

Cirrhosis of the Liver (8 Cases). In patients with cirrhosis of the liver with anemia there is a tendency toward macrocytosis of the red blood cells. In those patients who have, in addition to the primary hepatic insufficiency, actual loss of blood, the picture of hemorrhage with small red blood cells becomes more prominent. The uncomplicated cirrhosis of the liver shows an increase in the number of cells in the bone marrow, with the point of inhibition at the megaloblast stage. The bone marrow resembles that of pernicious anemia in relapse.⁴⁰ After remission has been produced in hepatic cirrhosis with intensive liver extract therapy, the bone marrow resembles that of the normal individual. Two types are encountered, one with an increase in the total number of cells in the bone marrow, with inhibition in growth at the megaloblast stage, and a second type with a decrease in the total number of nucleated cells, with the inhibition at the primitive blast stage, as is seen in chronic nephropathy. When there is gross secondary hemorrhage, there may be a great decrease in the total number of cells per cubic millimeter (Cases 5 and 6, Table 1).

Acute and Chronic Hemorrhage (12 Cases). In the first stage of acute blood loss there is relative increase in the number of polymorphonuclear leukocytes and their precursors in the sternal marrow. During the first 24 hours there is a tendency for a depletion of the cells in the bone marrow, with a decrease in the total number. Later, when the leukocytosis is reflected in the peripheral blood, there is an increase in percentage of eosinophilic normoblasts, followed later by predominance of cells in the basophilic normoblast stage. This corresponds to the stage of reticulocyte increase in the peripheral blood and possibly represents depletion, through maturation, of the eosinophilic normoblasts. During the stage of active regeneration, the total number of cells in the bone marrow is increased. In chronic hemorrhage, and in the regenerative stage of acute hemorrhage the normoblasts are smaller than normal. Case 7 in Table 1 illustrates the condition 8 hours after an acute hemorrhage.

Hemolytic Anemia (5 Cases). In a case of hemolytic anemia of long standing there was a relative predominance of cells in the eosinophilic normoblast stage. There may be an increase in the total number of nucleated cells in the bone marrow, although a few cases of long standing have been noted in which the cellular content was only two-thirds normal.

Hodgkin's Disease (5 Cases). In Hodgkin's disease treated by Roentgen ray and accompanied by anemia, there was not an invasion of the marrow by foreign cells, but an actual decrease in the number of nucleated forms of all types. The cells which remain appeared to mature in an orderly manner (Case 2, Table 1). In lymphosarcoma and lymphatic leukemia there was invasion of the marrow with neoplastic cells.

Chronic Nephritis: Nephropathy (10 Cases). The bone marrow in chronic nephritis is quite characteristic. There is an increase in number and relative percentage of cells in the primitive blast stage (Case 3, Table 1). These cells are sometimes mistaken for lymphocytes, and the marrow at first may suggest invasion by lymphoblastoma cells. Maturation is orderly, but only a few cells mature.^{4f} The red blood cells in the peripheral circulation show an abnormal number of forms measuring 7.5 microns, with but few larger or smaller. In 114 patients in whom there was a known nephropathy, the peripheral blood picture showed the characteristic red blood cell size abnormality (*e. g.*, about 25% less than 7.5 microns; 50%, 7.5 microns; 25% larger than 7.5 microns, instead of 33%, 34%, 33%, respectively). This peripheral blood change, related to the bone marrow change, appears quite early in the disease, before gross kidney dysfunction is apparent by the usual clinical tests.

Myelophthisic Anemia (19 Cases). In the myelophthisic anemias, as for example leukemia, the total nucleated cell number may be very high, depending on the size of the cells. In chronic myelogenous leukemia the maximum count of 864,000 nucleated cells per c.mm. was noted. In chronic lymphatic leukemia the maximum of 1,380,000 per c.mm. was found; in monocytic leukemia, 408,000 per c.mm.; in myeloblastic, or blast leukemia, the count may be relatively low in some patients (264,000 per c.mm.), although in others the marrow may be extremely cellular (1,872,000 per c.mm.). The disease is characterized by an increase in the number of primitive blasts, but the red blood cells which do mature do so in an orderly manner in the bone marrow. In the blood stream a disproportionate number of nucleated red blood cells, as compared with reticulated forms, are seen. There is a tendency for the red blood cells in the marrow to predominate in the basophilic normoblast stage; frequently in absolute numbers greater than normal. There is a possibility that there is a delay in maturation at this stage (Cases 9, 10, 11, Table 1).

Infection. Three types of bone marrow were noted in 15 patients with infection and various grades of anemia. In patients with leukocytosis there was a relative increase in the leukopoietic tissue, with a corresponding reduction in erythropoietic tissue. In the case of bronchopneumonia (No. 12) mentioned in Table 1, there was a progressive fall in the red blood cell count from 5.7 to 4.5

millions per c.mm. in 7 days (see also gas bacillus infection, Case 13, Table 1). In those patients having infection without leukocytosis, one group had a reduction in the total number of cells, the leukopoietic and erythropoietic tissue being proportionally affected (Case 14, Table 1). A second type showed an accumulation of red blood cells at the basophilic normoblast stage (Case 15, Table 1).

In infection, the stage of delay or "block" in the development of the red blood cells is the basophilic normoblast.

Discussion. On the basis of the stage of "block of growth" of the red blood cells in the sternal bone marrow, anemias may be classified as follows:

1. Inhibition of development in the primitive blast stage. Chronic nephritis (nephropathy): aplastic anemia.

2. Inhibition at megaloblast stage. Pernicious anemia; cirrhosis of the liver; most macrocytic anemias.

3. Inhibition delay at normoblast stage. Leukemia: infection.

The first group does not respond to any known specific therapy. The second responds to liver extract or stomach extract. The third form appears to be the result of factors other than deficiency, and responds to correction of the primary cause.

The study of the bone marrow suggests that red blood cells attain their size (stroma?) in the megaloblast stage, while most of the hemoglobin deposition appears to take place in the normoblast stage. Delay in development at the megaloblast stage causes the cells to become larger whereas passing rapidly through this stage is reflected in the small size of the red blood cells. The shorter the time spent in the normoblast stage, the greater the hemoglobin deficiency of the mature cell.

The quantitative studies of the cells of the bone marrow show that the organ is extremely labile and that it is difficult to describe a "normal" in terms of numbers of cells of any type in each cubic millimeter. The physiologic variations cover a wide range and evidently change takes place fairly rapidly in response to external requirements. The condition at death probably represents the extreme or end result of a tendency which has been present during the course of the disease. It is only when the same tendency has been noted in many cases, that one can generalize about a disease. Thus, while in the hypoplastic anemia of nephritis the primitive blasts grow, but tend to accumulate as such without a corresponding growth of the succeeding stages, in pernicious anemia or cirrhosis of the liver the growth process tends to be checked at the megaloblast stage.

Summary and Conclusions. 1. A method for counting the number of cells per cubic millimeter of a specimen of bone marrow is given.

2. The average normal sternal bone marrow is from 900,000 to 1,000,000 nucleated cells of all types per c.mm.

3. The distinct morphologic stages in the development of red

blood cells are (a) primitive blast, (b) megaloblast, (c) basophilic normoblast, (d) eosinophilic normoblast, (e) reticulocyte, (f) granule red blood cell, (g) mature erythrocyte.

4. The predominant stage varies with physiologic and pathologic changes.

5. Inhibition of growth is noted at the primitive blast stage in aplastic and hypoplastic anemia (nephropathy): at the megaloblast stage in the macrocytic anemias (pernicious anemia; cirrhosis of the liver): at the normoblast stage in leukemia and infection.

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HEREDITARY PSEUDO-HEMOPHILIA.

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AN hereditary hemorrhagic diathesis, presenting features distinctly different from those of true hemophilia, is being recognized with increasing frequency. The clinical features consist of recurrent hemorrhages from the nose, gums, gastro-intestinal tract, or uterus which may begin spontaneously or as a result of minor trauma. Hematuria, hemoptysis and hemarthrosis may occur. The bleeding may be mild or severe and is not infrequently fatal, but tends to be more profuse in younger patients and to diminish in severity with advancing age. Intracutaneous hemorrhage or purpura is not common, although the patients may bruise easily and bleed profusely from small cutaneous injuries. The manifestations may be present at birth or appear in infancy, but not infrequently are delayed until later childhood or adolescence. The most constant hematological features are a prolonged bleeding time with a normal platelet count.

Both males and females are affected by the disease and it may be transmitted by either sex directly to their sons and daughters. von Willebrand,^{20a, b} in a study of a large family, has determined it to be a dominant sex-linked Mendelian characteristic. Buckman⁴ found the disease transmitted directly by the males through 4 generations of a family, and Giffin⁷ records a case (Case 3) in which direct transmission by females occurred through 4 generations. Little and Ayres¹³ record the disease in 2 sisters in the fifth generation of a

family of bleeders, and Farber⁶ found 14 males and 11 females affected among 100 members of 5 generations. Minot¹⁴ reported 5 cases in 2 families in which the transmission was through the male, but both males and females were affected. The occurrence of the disease in the Negro has been recorded by Bailey and McAlpin.²

The case studied by Rothman and Nixon,¹⁷ as well as several of the other reported cases, had a poorly retractile clot in addition to the prolonged bleeding time and in those cases recorded by Buckman,⁴ Rosenthal,¹⁶ and Austin and Pepper¹ the coagulation time was also prolonged. Hemarthrosis was found by Weeks¹⁹ and Rosenfeld.¹⁵

Glanzmann⁸ studied 8 families with this hemorrhagic taint and termed it "hereditary hemorrhagic thrombasthenia" and Kugel-mass,¹¹ including the condition among the hemorrhagic diseases of children, has accepted this nomenclature. Buckman,⁴ however, found that a suspension of platelets from such a patient produced as rapid coagulation of hemophilic blood as did the platelets from a healthy individual, and Glanzmann was able to produce coagulation in normal platelet-free plasma by the addition of platelets from one of his cases, although the resultant clot did not retract properly. These results suggest that the platelets are normal, not only numerically but qualitatively as well, so that the terms "thrombasthenia" and "constitutional thrombopathy" are not applicable.

Under the term "hereditary pseudo hemophilia" Handley and Nussbrecher⁹ present a detailed family history and a discussion of the genetics of a family of bleeders. The transmission and hematological features were typical of hemophilia but the disease appeared in women. While the bleeding time was normal, the coagulation time was prolonged, and the question was raised as to whether these patients represent homozygous hemophilic females or cases similar to those recorded as pseudo-hemophilia by von Willebrand. The authors were inclined toward the latter view. Other unusual cases of hereditary hemorrhagic diseases have been reported, including those of hereditary thrombopenic purpura by Witts,²¹ Rosenfeld,¹⁵ Austin and Pepper,¹ and Krömeke,¹⁰ as well as cases of spontaneous hemophilia by Boggs³ and others.

Case Abstracts. CASE 1.—At the age of 3 (1893) this patient began passing blood per rectum and these spontaneous hemorrhages recurred at irregular intervals for several years. Between 6 and 12 he had frequent, profuse hemorrhages from the gums, many of which followed the loss of deciduous teeth, while others began spontaneously. At the age of 11 he was almost exsanguinated after a minor scalp injury. When 13 he began to have epistaxes, a tendency which persisted as the most troublesome feature for many years. At the age of 24 he was given 30 cc. of horse serum intramuscularly, which seemed to control the bleeding. About 2 years later a second intramuscular injection of 40 cc. was followed by a severe foreign protein reaction and cessation of the hemorrhagic tendencies, so that for a few years he was relatively free from symptoms. In 1918, the bleeding again became more severe and in 1923 he was admitted to this hospital after a continuous

hemorrhage from the nose and gums of 11 days' duration. Nothing of significance was found on physical examination except a palpable spleen and evidences of hemorrhage and anemia. The hemoglobin was 25% and the erythrocyte count was 1,120,000. The patient's blood was Type II (Moss). He was given a transfusion and intramuscular injections of whole blood, with some diminution of the bleeding, but it had not entirely ceased at the end of 17 days when he left the hospital against advice.

He continued to bleed occasionally and in January, 1925, he became unusually weak, began to pass tarry stools and to vomit blood, and was readmitted to the hospital with a hemoglobin of 23% and an erythrocyte count of 1,400,000. He bled profusely, from the nose, gums and gastrointestinal tract for several weeks, during which time he received 3 transfusions of 500 cc. each (Group IV, Moss), and 3 intramuscular injections of whole blood. The hemorrhage ceased and, when discharged from the hospital, the hemoglobin was 73% of normal, the erythrocytes 4,200,000.

From 1925 to 1930 he had innumerable minor hemorrhages but hospitalization was necessary on only one occasion during this period. When he returned in 1930, many therapeutic measures were tried in an attempt to control the bleeding. A 500 cc. transfusion of Type II blood was given without effect (previous transfusions, Moss, Type IV). Three intramuscular injections of 20 cc. of blood were given at daily intervals without appreciable effect on the bleeding. Fibrinogen had no effect when given subcutaneously in 1 cc. doses at daily intervals for 5 days. Daily intramuscular injections of coagulin (7 to 20 cc. each) for 6 days gave no relief. The patient was found to be sensitive to horse serum and small subcutaneous injections caused some urticaria and a sense of constriction in the chest, but had no definite effect on the bleeding. Two subsequent intramuscular injections of 18 and 20 cc. of horse serum were given without a reaction and without effect on the bleeding. A transfusion of 250 cc. of Group IV blood was given and was followed by a feeling of chilliness and by cessation of the bleeding.

During the subsequent 5 years the patient was in the hospital on 6 occasions, each admission being preceded by prolonged uncontrollable bleeding from the nose and gums. Following the last admission, he was supplied with Moccasin Snake Venom Solution which was administered by his local physician. He received 12 semi-weekly injections which seemed to control the mild hemorrhagic symptoms. Four weeks later more severe hemorrhagic manifestations appeared which were not affected by 4 injections of the same snake venom. He was recalled to the hospital and, although he was not bleeding, snake venom was administered so as to study its effect on the bleeding time. The material was administered twice weekly in doses of 0.4 cmm, 0.8 cmm., and 4 injections of 1 cmm. each. The bleed-

TABLE 1.—HEMATOLOGIC FEATURES.

	Platelets.	Bleeding time, minutes.	Coagu- lation time, minutes.	Clot retrac- tivity.	Constrictor test.	Fragility test hemolysis.		Pro- thrombin time, minutes.
						Began.	Complete.	
5/ 2/23 . . .	610,000	25+	4	Good	.	42	32	15-19-19-19
2/ 9/25 . . .	960,000	6	5	Good	Negative	44	36	8-9-9-12
4/16/25 . . .	545,000	25+	5	Good	Negative	44	32	6-7-7-8
9/19/25 . . .	290,000	3½	5	Good	Negative	44	36	5-5-6-8
10/30/28 . . .	0.4	5 hrs. +	16	Good	Negative	42	34	15-16-17
9/20/29 . . .	0.4	30+	6	Good	1+	40	30	10-10-10
10/22/29 . . .	0.55	60+	7	Good	1+	44	34	6-6-7
9/24/30 . . .	0.6	45+	4	Good	3+	40	32	9-8-8-9
9/ 9/31 . . .	0.4	30+	4	Good	1+	44	34	17-11-11-15
12/ 2/32 . . .	0.32	30+	5	Good	Negative	40	28	23-19-19
5/31/34 . . .	0.4	15+	5	Good	Negative	44	34	4-5-5-6
4/11/35 . . .	0.56	15+	6	Good	1+	44	32	
1/29/36 . . .	0.64	30+	6½	Good	Negative	44	34	13-13-14-16

Platelets were determined by the Van Allen Thrombocytoerit Method¹³ in 1928 and on all subsequent occasions.

ing time was not affected, but mild epistaxis and bleeding from the gums began during the course of treatment. A transfusion of 500 cc. of Group IV blood controlled the bleeding but did not affect the bleeding time.

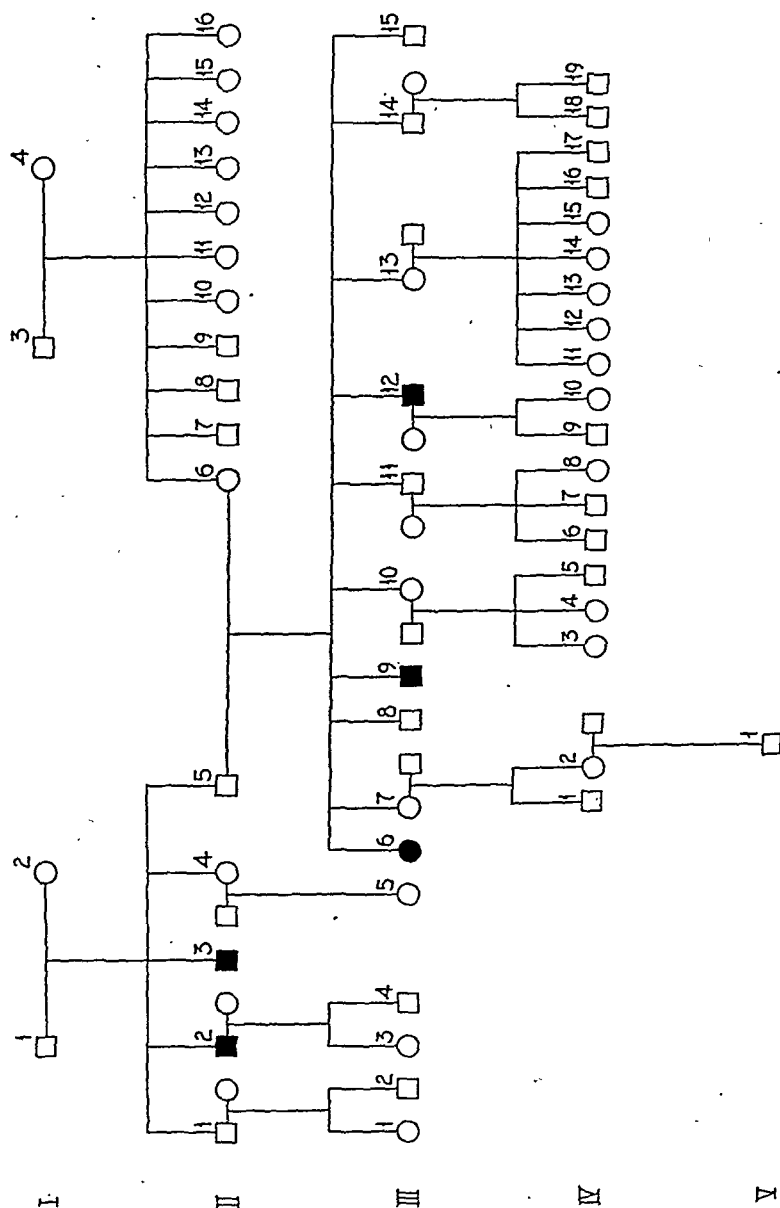


CHART I.—FAMILIAL HEMORRHAGIC TENDENCIES IN CASE 1.

During the 13 years this patient has been under observation there have been no purpuric hemorrhages into the skin, and although he has bruised more easily than normal there has never been an extensive hematoma. Hematuria was never noted. The bleeding was predominantly from the

mucous membranes of the nose, mouth and gastro-intestinal tract, and, except for those times when the hemorrhages were especially severe, it seemed to occur from only one location at a time.

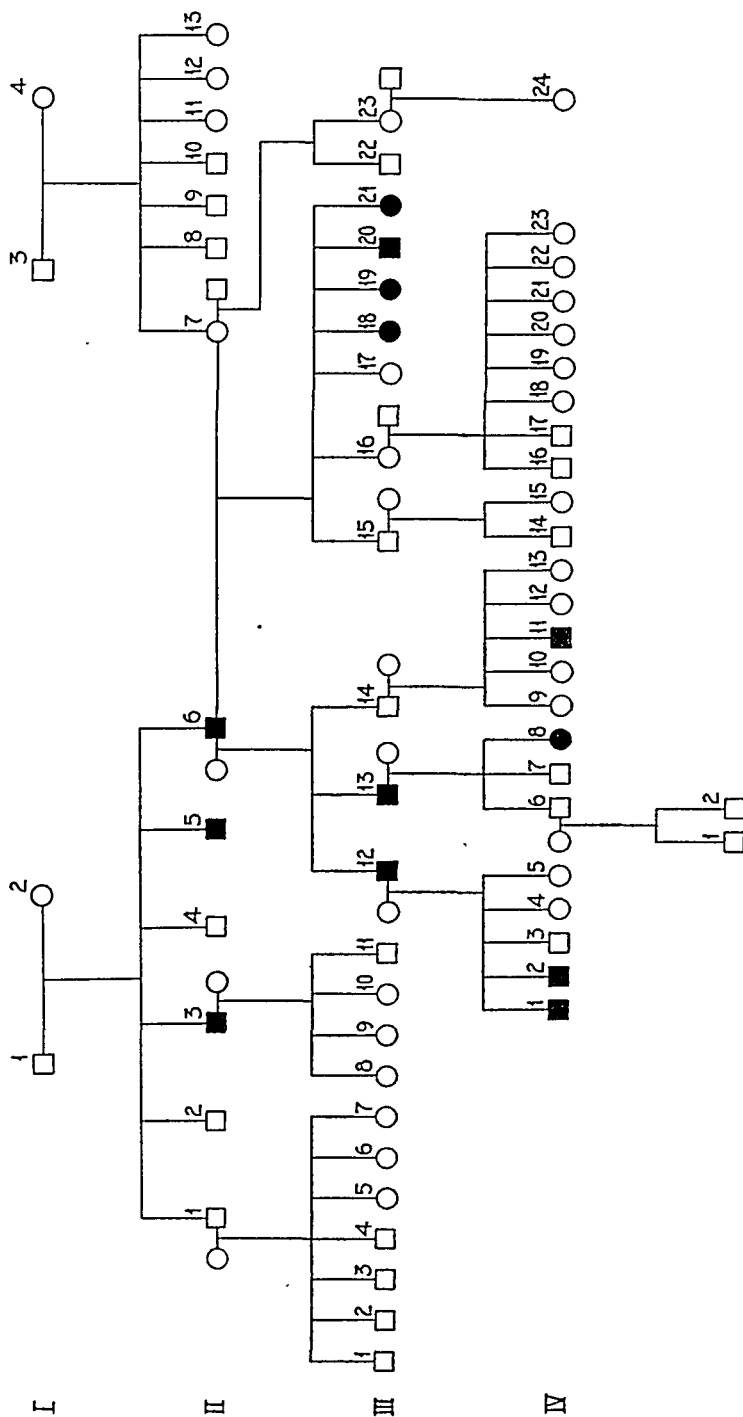


CHART II.—FAMILIAL HEMORRHAGIC TENDENCIES IN CASE 2.

The most consistent hematologic feature was the prolonged bleeding time (Duke's) which was present on all but 2 occasions (Table 1). There was, however, no correlation between the length of the bleeding time and

the severity of the hemorrhage. The coagulation time was normal on all but one trial and this prolongation occurred during a period of especially severe hemorrhage. The clot retracted normally on all occasions and the platelets were normal or increased on every examination. The results of the constrictor test were not uniform and the prothrombin time varied, being definitely prolonged on four occasions. The fragility of the erythrocytes was consistently normal.

Therapy. Adrenalin packs have been used to combat the nasal hemorrhages on innumerable occasions but the bleeding has never been entirely controlled by this means. Local applications of fibrinogen and thromboplastin have been of no avail, but coagulen (Ciba) has given slight relief. These substances when given parenterally and fibrinogen when given by mouth have had no effect. The hemostatic effect of horse serum has not been consistent. According to the patient's statement, hemorrhage ceased after the first injection, but even better results were obtained after the second, which produced a severe serum sickness. Urticaria and serum sickness were induced in the patient while under our observation, but no relief was obtained and subsequent injections of serum after desensitization of the patient were of no benefit.

Transfusions have been most reliable in controlling the bleeding, but even this had but a very transient effect during a severe hemorrhage. Slight febrile reactions were experienced by the patient after some transfusions, but the presence or absence of these mild reactions apparently played no part in the effectiveness. During the periods when there was only slight bleeding, complete cessation frequently occurred after transfusions. Intramuscular blood had no effect during the severe hemorrhages but was of some benefit when the bleeding was less severe.

The hemorrhagic tendency in this family is presented in Chart I. It will be noted that two brothers of the patient's father showed this tendency. Their bleeding was relatively mild and the father himself was unaffected. The patient presented in this communication is represented as III-9 in the chart. His sister (III-6) had severe hemorrhagic manifestations and died at 17 years of age from uterine hemorrhage. A younger brother (III-12) had hemorrhagic manifestations identical to those of the patient and died from gastro-intestinal hemorrhage in November, 1935.

CASE 2.—A white female, aged 22, gave a history of having bruised easily all of her life. She had spontaneous ecchymoses and epistaxis, and recently her menstrual periods had become unusually profuse. None of the hemorrhages had been severe enough to be alarming. On admission to the hospital there was a large hematoma over the left malar eminence, which the patient stated had appeared spontaneously. The remainder of the physical examination and history is irrelevant. The bleeding time varied from $7\frac{1}{2}$ to $11\frac{1}{2}$ minutes, but the coagulation time was normal. The platelets were normal, the clot retracted properly and the fragility of the erythrocytes was normal. The constrictor test was slightly positive.

The family history of bleeding is presented in Chart II. Both the patient's father and mother had been married twice and the hemorrhagic tendency appears to be transmitted through the father. The patient (III-21) was the youngest of her family. All the affected members have shown relatively mild hemorrhagic tendencies. Both males and females have been involved, transmission has occurred only through the males and, in one instance (IV-II) the disease was transmitted by an apparently unaffected male. A very similar family of bleeders has been reported by Lane.¹²

Discussion. The hematological features of these 2 cases are the same, and the points of difference seem to lie mainly in the severity

of the hemorrhagic manifestations. Although it is possible that we are dealing with different clinical entities, such a conclusion does not seem justifiable when the essential points of difference lie only in the severity.

The hematological features in these, as well as in the previously reported cases, are the prolonged bleeding time, the normal or high platelet determination and the normal coagulation time. The results of the constrictor test, the prothrombin time and the clot retractility vary from one case to another and from time to time in the same patient. These are found to be normal in most cases, but because of their variability cannot be considered as essential points in the diagnosis.

Therapeutic measures carried out during periods of severe bleeding are not satisfactory. Transfusions seem to give the best results, although the benefits are transient at the best. The results of foreign protein therapy were inconsistent and of doubtful reliability. During the less severe hemorrhagic episodes both transfusion and intramuscular blood controlled the bleeding, while the other procedures which were tried did not give convincing proof of their hemostatic ability. Transfusions, even though they controlled the clinical manifestations, did not affect the bleeding time.

The familial characteristics of the disease are beyond question; but the frequency with which females are affected, the transmission by males, and the direct transmission to sons or daughters are distinctly different from hemophilia. The hematological features of prolonged bleeding time and normal coagulation time are the reverse of those found in hemophilia.

The clinical features are quite similar to those of thrombopenic purpura, but the abundance of platelets and the normal syneresis in pseudo-hemophilia serve to distinguish the two conditions.

Since there is no apparent change in the platelets, either quantitatively or qualitatively, the term "thrombasthenia" does not seem applicable to these cases. Their classification as "hereditary hemorrhagic diathesis" describes the principal features, but is so broad and inclusive that it may lead to confusion at a later date when certain cases of hereditary bleeding are separated and reclassified as distinct entities. It seems better to adopt the terminology of von Willebrand and at least temporarily call them pseudo-hemophilia. This expresses no opinion as to the pathogenesis of the condition, implies a familial tendency and would tend to prevent confusion if these cases are eventually separated into more distinct clinical entities.

Conclusions. The hematological and familial features of 2 cases of hereditary pseudo-hemophilia have been presented.

The prolonged bleeding time with a normal platelet determination, coagulation time and clot retractility, are the predominant features.

The results obtained with various forms of therapy have been presented, and of these, transfusions were found to be most effective.

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**PHYSIOLOGIC EFFECTS OF ACETYL-BETA-METHYLCHOLINE
(MECHOLYL) AND ITS RELATIONSHIP TO OTHER DRUGS
AFFECTING THE AUTONOMIC NERVOUS SYSTEM.***

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SINCE the original studies on the various choline derivatives by Hunt and Taveau⁵ in 1911, there has been a great renewal of interest in these compounds. One of the most active of the cholines, acetyl-beta-methylcholine (mecholy), has been shown by Starr, Elsom, Reisinger,¹² Weiss and Ellis¹³ to be many times as active in its physiologic effects as acetylcholine. Our interest in this drug derives from a series of studies at present in progress on the interrelationships of the various drugs which affect the autonomic nervous system. Acetyl-beta-methylcholine was utilized because of its rapidity and uniformity of action, and its apparently "pure" parasympathetic effect.

* Aided by Grants from the Commonwealth of Massachusetts and the Rockefeller Foundation.

The pronounced parasympathetic effect of acetyl-beta-methylcholine, in addition to its ability in causing a lowering of blood pressure and its absence of sympathetic effect, has been demonstrated by many workers. Starr, Elsom, Reisinger,¹² Page⁸ and others have given excellent descriptions of the effect of acetyl-beta-methylcholine in normal and in certain clinical conditions.

Material and Technique. Twenty subjects, 18 of whom represented various types of dementia præcox and 2 paretics, were studied. These subjects presented no evidence of any definite physical disease. They were very passive, unemotional, and lay perfectly quiet throughout the entire experimental procedure. They came to the laboratory in the morning, without breakfast, and were allowed to rest for about a half hour before the experiments were begun. No preliminary anesthesia was used in any case. In most instances, acetyl-beta-methylcholine was administered in 30 mg. doses subcutaneously. Observations of acetyl-beta-methylcholine alone and when combined with atropine, sodium amytal, phenyliso-propylamin (benzedrine), and adrenalin were made.

Effects of Subcutaneous Administration of Acetyl-beta-methylcholine (30 mg.). Within a minute following the injection, flushing of the face which soon spread to the chest and back occurred. This was soon followed by perspiration of the face, injection of the conjunctivæ, spreading perspiration to the chest and back which increased to a moderate or marked degree and which reached its acme

TABLE 1.—THE EFFECT OF SUBCUTANEOUS ADMINISTRATION (15-40 MG.) OF ACETYL-BETA-METHYLCHOLINE (MECHOLYL) ON 20 PSYCHOTIC SUBJECTS.

Patient.	Diag.	Dose, subcut. in mg.	Control period.			Condition at height of test.				Condition at end of test.				Reaction: Flush, perspiration, rhinorrhea, lacrimation.
			B. P.	Pulse rate	S. F. P.	B. P.	Pulse rate.	S. F. P.	Time in min.	B. P.	Pulse rate.	S. F. P.	*Time in min.	
J. P. S.	D. P.	30	120/66	72	120	80/44	108	180	24	94/60	60	120	19	Slight.
A. McN.	D. P.	30	102/76	92	170	90/60	120	200	1	76	124	155	12	Marked.
C. P.	D. P.	40	104/76	88	165	90/70	120	200	5½	90	88	190	18	Slight.
J. S.	D. P.	30	150/84	76	150	106/64	120	230	11	118/66	84	160	35	Moderate to marked.
J. B.	D. P.	30	126/70	88	115	96/58	112	175	4	116/68	92	135	32	Moderate to marked.
J. P.	D. P.	30	106/54	88	120	78/50	120	200	4	120/60	92	130	14	Marked.
E. B.	D. P.	30	118/86	92	85	114/70	128	140	6	120/80	92	75	19	Marked.
H. B.	G. P.	30	136/82	88	160	100/60	140	300	22	124/70	96	170	47	Marked.
A. Fr.	D. P.	30	100/50	80	150	74/48	108	240	2	90/56	88	160	26	Marked.
H. P.	D. P.	30	116/80	76	120	86/50	132	190	4	96/58	92	200	27	Marked.
D. F.	D. P.	30	122/86	80	125	82/56	130	185	10	86/58	116	125	16	Marked.
J. M.	G. P.	30	136/90	84	170	100/60	128	280	4	116/76	100	200	18	Moderate to marked.
J. McG.	D. P.	30	124/90	120	190	88/44	148	210	3	110/60	120	180	19	Moderate.
E. B.	D. P.	30	108/70	80	100	70/60	96	200	3	80/60	92	120	25	Marked.
J. C.	D. P.	30	138/70	68	120	106/60	120	240	5	116/70	72	120	35	Marked.
J. G.	D. P.	30	110/70	68	80	74/48	112	110	3	94/60	88	80	35	Moderate to marked.
M. G.	D. P.	30	134/90	84	90	80/56	100	145	4	110/70	84	96	26	Marked.
H. H.	D. P.	15	106/70	92	150	94/2	100	190	5	116	100	...	16	Moderate.
A. F.	D. P.	30	98/68	72	90	76/2	100	120	3	90/60	74	125	30	Marked.
A. McN.	D. P.	30	110/80	96	...	76/48	140	...	3	92/70	128	...	13	Marked.

* Time from the injection of the acetyl-beta-methylcholine.

Key to this and following tables:

D. P. = Dementia præcox; G. P. = General paresis; B. P. = Blood pressure; S. F. P. = Spinal fluid pressure.

in about 5 minutes and gradually receded. Perspiration rarely extended beyond the epigastrium and on the back never beyond the level of the hips. In most cases rhinorrhea and salivation occurred in moderate to marked degree. Within a minute following the injection, the pulse increased, reaching its height in most instances

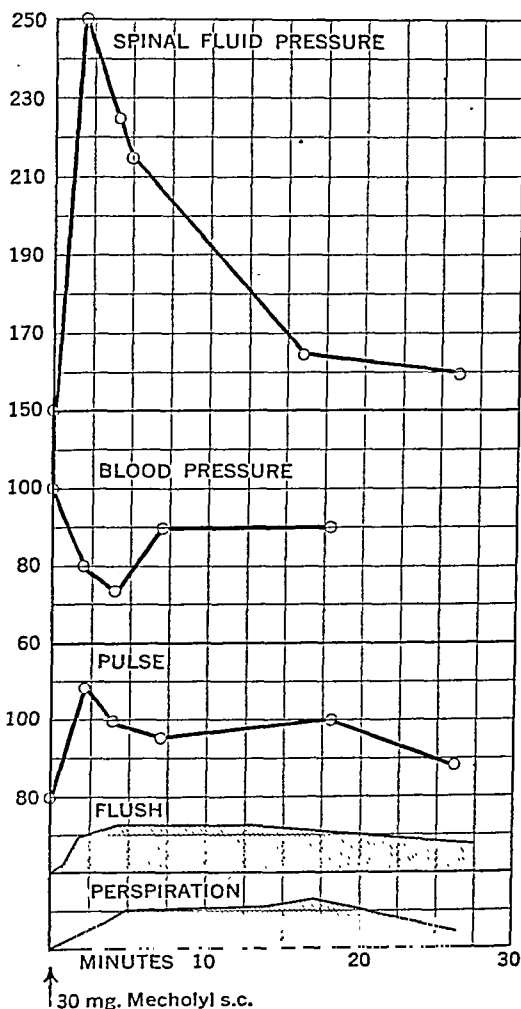


CHART I (Dementia præcox).—The effect of subcutaneous administration of mecholyl (30 mg.) on the blood pressure, pulse rate and spinal fluid pressure. This subject showed a marked flushing of the face and chest and marked perspiration of the face and upper part of the body.

within 4 minutes. In most cases, it did not return to its original level until more than 10 minutes following the injection had elapsed. In no case was there observed an original slowing of the pulse rate. In 1 case, the pulse returned to a slightly lower than the basal level several minutes after the injection. The increase in pulse rate in

the 20 cases varied from 8 to 56 beats per minute. Usually the blood pressure dropped within a minute following the injection, the drop varying from 4 to 54 mm. of mercury, reaching its minimum at about the same time the pulse was at its maximum. The subjects were observed for at least 20 to 30 minutes, at which time the vaso-motor and secretory manifestations had usually disappeared.

TABLE 2.—THE EFFECT OF A SMALL DOSE OF ACETYL-BETA-METHYLCHOLINE (5.0 MG. SUBCUTANEOUSLY) ON 5 DEMENTIA PRÆCOX PATIENTS AND 1 PARETIC.

Patient.	Diag.	Control period.		Condition at height of test.			Condition at end of test.			Reaction.
		B. P.	Pulse rate.	B. P.	Pulse rate.	Time in min.	B. P.	Pulse rate.	Time*	
G. T.	D. P.	118/80	72	128/80	92	3	118/70	74	8	Slight flush of face.
R. R.	G. P.	118/88	66	124/100	83	2	112/80	80	12	Subjective flushing of face.
C. P.	D. P.	114/80	80	120/80	84	6	118/82	80	11	Subjective flushing of face.
A. F.	D. P.	110/80	68	84/7	92	2	108/78	68	14	Slight flush of face.
J. B.	D. P.	120/70	92	134/70	104	3	120/68	68	18	Subjective flushing of face.
H. H.	D. P.	128/80	80	136/82	100	2	128/76	80	7	No flushing of face.

* Time from the injection of the acetyl-beta-methylcholine.

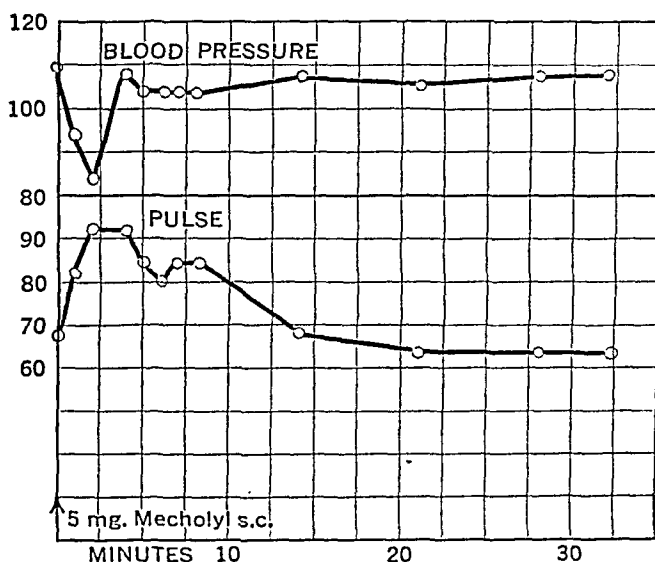


CHART II (Dementia præcox).—The effect of a small dose (5 mg.) of mecholy subcutaneously. This dose was sufficient to cause a moderate drop in blood pressure and a moderate rise in pulse rate.

The cerebrospinal fluid pressure rose definitely in every case, the increase varying from 30 to 140 mm. of water. The maximum spinal fluid pressure usually coincided with the minimum blood pressure.

Although several of the patients were obviously uncomfortable at the height of the mecholy reaction, no changes in their mental reaction or in their behavior were observed during the entire experiment (Table 1, Chart I).

Effect of Acetyl-beta-methylcholine on the Gastro-intestinal tonus and Motility. Experiments on this subject will furnish the material for a separate communication. Mecholyl has a very marked effect upon the tonus and peristalsis of the gastro-intestinal tract. It

TABLE 3.—THE EFFECT OF THE ADMINISTRATION OF ACETYL-BETA-METHYLCHOLINE FOLLOWED BY ATROPINE.

Patient.	Diag.	Control period.		Mecholyl.				Atropine				Condition at end of test.		
		B. P.	Pulse rate.	Dose, mg.	B. P.	Pulse rate.	Time in min.	Dose, gr.	B. P.	Pulse rate.	Time in min.	B. P.	Pulse rate.	*Time in min.
J. B.	D. P.	120/70	100	30 (i. m.)	88/60	124	7	1/50 (i. v.)	130/84	120	9	118/66	124	16
A. F.	D. P.	80/46	80	30 (i. m.)	70/38	108	5	1/100 (s. c.)	86/56	80	7	80/50	76	21
J. G.	D. P.	106/74	68	30 (i. m.)	94/50	140	17	1/100 (s. c.)	110/70	96	18	110/74	68	25
M. G.	D. P.	120/76	88	20 (s. c.)	92/50	112	2	1/100 (s. c.)	84/?	96	3	100/?	72	23

* Time from the injection of the mecholyl.

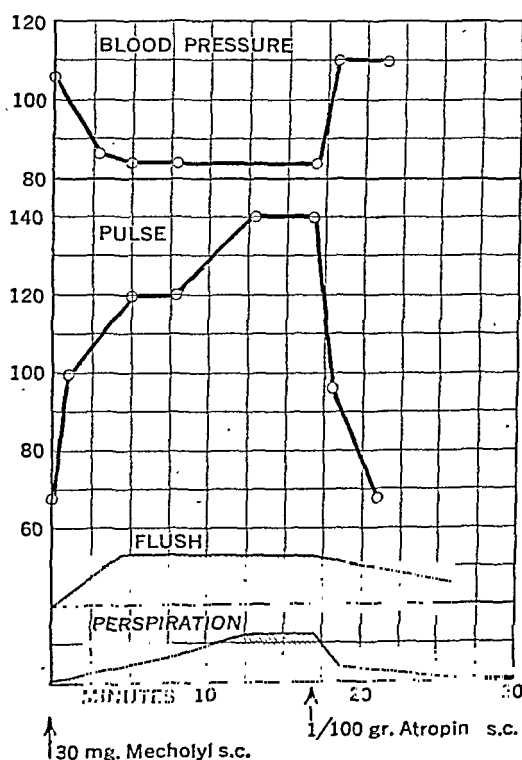


CHART III (Dementia præcox).—The typical counteracting effect of atropine on the mecholyl reaction. Note the almost immediate return of the blood pressure and pulse rate to their original levels following the atropine injection.

increases these functions of gastro-intestinal activity very markedly. On the atonic gastro-intestinal tract it exercises a rapid and more or less prolonged effect.

Effect of Small Doses of Acetyl-beta-methylcholine (5 mg. Subcutaneously). In 5 dementia præcox subjects and 1 paretic, 5 mg. of mecholyl was injected subcutaneously. The pulse increased in every case from 4 to 24 beats per minute. One case showed

TABLE 4.—EFFECT OF SIMULTANEOUS ADMINISTRATION OF ACETYL-BETA-METHYLCHOLINE AND ATROPINE.

Patient	Diag.	Control period.		Height of combined drug reaction.					Condition at end of test.		
		B. P.	Pulse rate.	Dose.		B. P	Pulse rate.	Time in min.	B. P.	Pulse rate.	Time in min.
				Mecholyl, mg.	Atropine, gr.						
H. H.	D. P.	146/84	84	30 (s. c.)	1/200 (s. c.)	134/76	120	2			
					1/200 (s. c.)	146/84	112	*1	142/88	88	12
J. S.	D. P.	140/88	92	50 (i. m.)	1/100 (i. v.)	136/80	120	6	120/80	106	39
R.	D. P.	124/76	124	30 (i. m.)	1/200 (s. c.)	96/50	148	2			
					1/200 (s. c.)	136/70	116	*1	112/60	112	12
J. C.	D. P.	108/60	88	30 (i. m.)	1/200 (i. m.)	120/50	120	2			
					1/200 (i. m.)	110/68	78	*2	108/66	68	10

* Time from second dose of atropine.

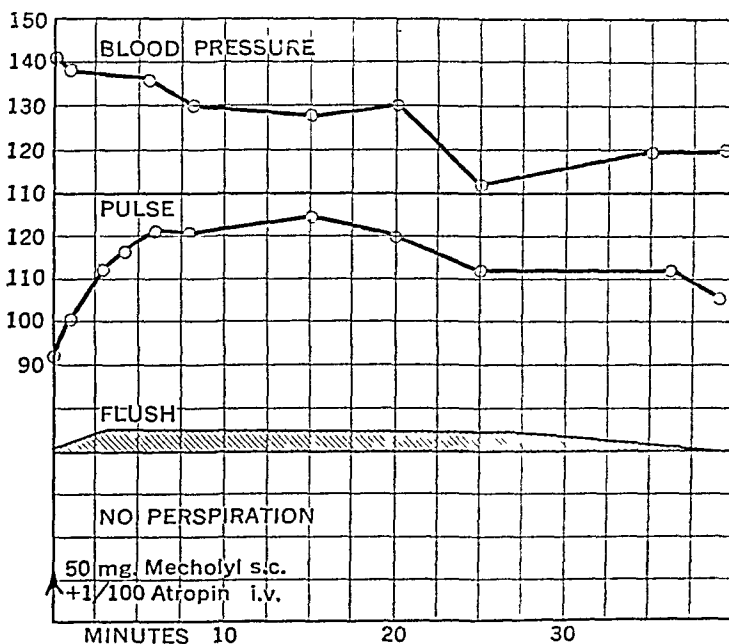


CHART IV (Dementia præcox).—The simultaneous administration of a large dose of mecholyl subcutaneously and a moderate intravenous dose of atropine. In this case, although the atropine was sufficient to prevent the secretory responses of mecholyl it was unable to prevent a drop in blood pressure.

a secondary slowing of the pulse. In 5 of these subjects the blood pressure rose slightly, varying from 8 to 14 mm. of mercury. In the other case, the blood pressure showed a fall of 26 mm. of mercury. Except for slight flushing of the face, no other visible effects of the drug were noted. As a control observation, plunging of

the needle under the skin of these subjects caused only a momentary or no change in pulse rate or blood pressure (Table 2, Chart II).

Effect of Acetyl-beta-methylcholine Followed by Atropine. In 4 of the dementia præcox subjects, the mecholyl reaction was allowed to reach its height, at which time atropine was administered, $\frac{1}{100}$ gr. subcutaneously in 3 cases and $\frac{1}{50}$ intravenously in the other case. Following the atropine injection, within 1 or 2 minutes perspiration and other concomitant phenomena became very mild or completely disappeared. The pulse rate fell and the blood pressure rose to a level slightly higher than its original in 3 of the cases. In the fourth case, the blood pressure failed to rise; in fact, it dropped to a slightly lower level (Table 3, Chart III).

Simultaneous Administration of Acetyl-beta-methylcholine and Atropine. In 4 cases mecholyl and atropine were simultaneously administered in various doses. In 1 case, 30 mg. of mecholyl subcutaneously and gr. $\frac{1}{200}$ of atropine subcutaneously caused a drop in blood pressure of 12 mm. of mercury, a rise in pulse rate, and an otherwise moderate mecholyl reaction. A repetition of an injection of gr. $\frac{1}{200}$ atropine 7 minutes later almost promptly nullified the vasomotor and secretory manifestations of mecholyl and caused a fall in pulse rate and a rise in blood pressure to the original level. In the second case, 50 mg. mecholyl intramuscularly and $\frac{1}{100}$ gr. of atropine intravenously caused a drop in blood pressure of only 4 mm. of mercury, a rise in pulse rate, and practically no visible phenomena. In the third case, 30 mg. of mecholyl intramuscularly and $\frac{1}{200}$ gr. of atropine subcutaneously produced a fall in blood pressure of 28 mm. of mercury, a rise in pulse rate, and a marked vasomotor and secretory reaction. The blood pressure returned to a higher than the original level; the pulse rate fell to slightly below the control level; and the skin and secretory reaction completely disappeared, when another injection of $\frac{1}{200}$ gr. subcutaneously of atropine was given. In the fourth case, 30 mg. of mecholyl intramuscularly and gr. $\frac{1}{100}$ of atropine intramuscularly produced a rise in blood pressure of 12 mm. of mercury, a rise in pulse rate, and a slight vasomotor and secretory reaction which was immediately nullified by another injection of gr. $\frac{1}{200}$ of atropine intramuscularly. The pulse rate now fell to slightly below its original level. These experiments definitely indicate the pronounced antagonism of the two drugs, the combined reaction depending upon the quantities and the route of administration (Table 4, Chart IV).

Administration of Atropine Followed by Acetyl-beta-methylcholine. The remarkable antagonism of the two drugs was now demonstrated in 3 cases when mecholyl (30 mg.) was given after large doses of atropine. In none of these cases were any visible manifestations of mecholyl noted. In 1 case, gr. $\frac{1}{50}$ of atropine intravenously caused a rise in pulse rate and no change in blood pressure. Now 30 mg. of mecholyl subcutaneously caused a fall in pulse rate and

a fall in blood pressure of 6 mm. of mercury. In the second case, $\frac{1}{50}$ of atropine intravenously caused a slight rise in blood pressure and a moderate rise in pulse rate. Thirty mg. of mecholyll now caused a fall in blood pressure of 24 mm. of mercury and a slight rise in pulse rate. In the third case, gr. $\frac{1}{50}$ of atropine subcutaneously produced no essential change in blood pressure or pulse. Following

TABLE 5.—THE EFFECT OF THE ADMINISTRATION OF ATROPINE FOLLOWED BY ACETYL-BETA-METHYLCHOLINE.

Patient.	Diag.	Control period.		Atropine.				Mecholyl.				Condition at end of test.		
		B. P.	Pulse rate.	Dose (gr.)	B. P.	Pulse rate.	*Time in min.	Dose (mg.)	B. P.	Pulse rate.	*Time in min.	B. P.	Pulse rate.	*Time.
H. B.	G. P.	118/74	100	1/50 (i. v.)	116/80	128	3	30 (s. c.)	110/72	120	4	116/74	108	1 hr. 7 min.
E. B.	D. P.	110/76	76	1/50 (i. v.)	114/70	104	4	30 (i. m.)	90/76	108	5	106/80	96	1 hr. 19 min.
J. P.	D. P.	120/70	84	1/50 (s. c.)	118/68	88	4	30 (s. c.)	114/72	92	8	106/70	86	30 min.

* Time from beginning of injection of first drug.

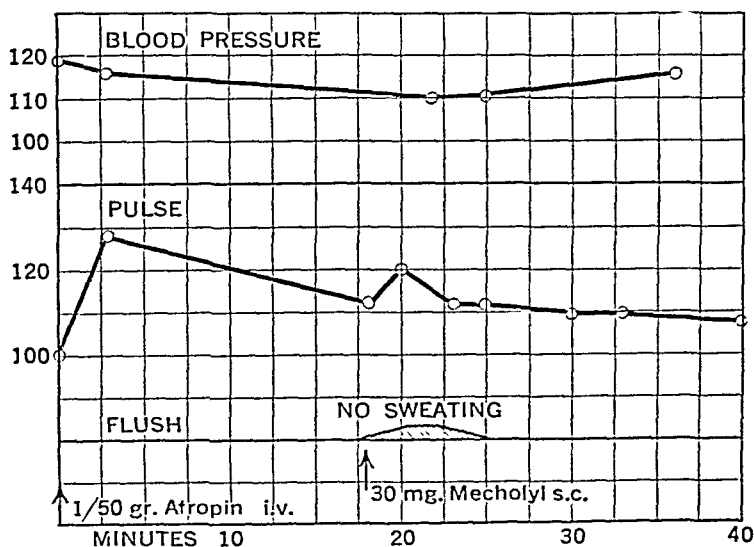


CHART V (Dementia præcox).—The effect of a large intravenous dose of atropine followed by a moderate dose of mecholyll. Here the atropine practically prevented the effect of the mecholyll reaction.

the injection of 30 mg. of mecholyll subcutaneously, the blood pressure fell 6 mm. of mercury and the pulse rose four beats per minute.

These results coincide with those made by other observers, who pointed out the absence of any nicotinic action in mecholyll as demonstrated by the inability of the drug to cause a rise in blood pressure after paralysis of the parasympathetic by atropine. The usual

moderate fall in blood pressure, however, caused by mecholyl is definitely diminished or prevented after preliminary administration of atropine (Table 5, Chart V).

Combined Effect of Sodium Amytal and Acetyl-beta-methylcholine. Since the anesthetic action of sodium amytal is held by some investigators to be due to a specific effect on the hypothalamus, we felt

TABLE 6.—THE EFFECT OF THE ADMINISTRATION OF SODIUM AMYTAL AND ACETYL-BETA-METHYLCHOLINE.

Patient.	Diag.	Control period.		Amytal.				Mecholyl.				Condition at end of test.		
		B. P.	Pulse rate.	Dose, gr.	B. P.	Pulse rate.	*Time in min.	Dose in mg.	B. P.	Pulse rate.	Time in min.	B. P.	Pulse rate.	*Time in min.
J. McG.	D. P.	126/80	116	0.7 (i. v.)	96/70	96	4	30 (s. c.)	56/40	104	5	86/7	92	30
J. M.	G. P.	144/90	78	0.7 (i. v.)	80/70	88	4	30 (s. c.)	62/7	104	11			
J. G.	D. P.	110/70	80	0.5 (i. v.)	96/68	76	3	30 (s. c.)	70/40	128	9	106	88	51
M. G.	D. P.	104/88	84	0.5 (i. v.)	86/60	84	4	30 (s. c.)	76/54	104	13	96/70	104	16

* Time from beginning of injection of sodium amytal.

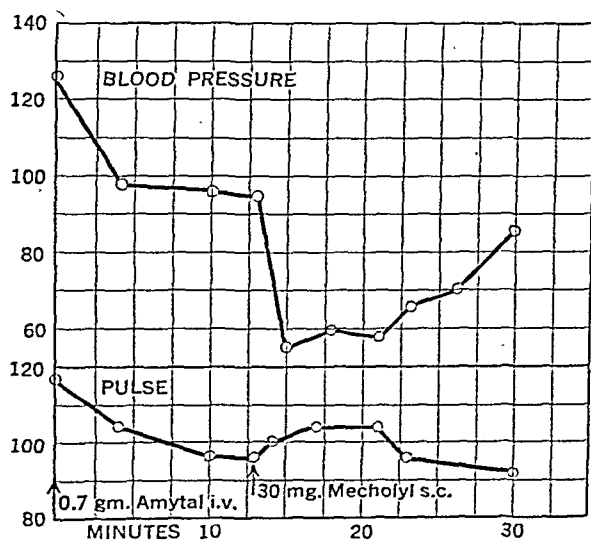


CHART VI (Dementia præcox).—The effect of the intravenous administration of amytal followed by subcutaneous injection of mecholyl. The effect of the two drugs on the blood pressure is additive.

it would be interesting to observe any altered effects of mecholyl during sodium amytal narcosis.

Three dementia præcox subjects and 1 paretic were narcotized by intravenous injections of sodium amytal (0.5 to 0.7 gm.). The subjects all fell soundly asleep during or immediately after the injection of the sodium amytal. In the first case, a fall in blood pressure of

30 mm. accompanied by a drop in pulse rate of 20 beats per minute occurred at the height of the amytal narcosis. The injection of 30 mg. of mecholyl now caused a greater fall in blood pressure accompanied by a slight rise in pulse rate. The drop in blood pressure caused by the injection of both drugs was 70 mm. of mercury.

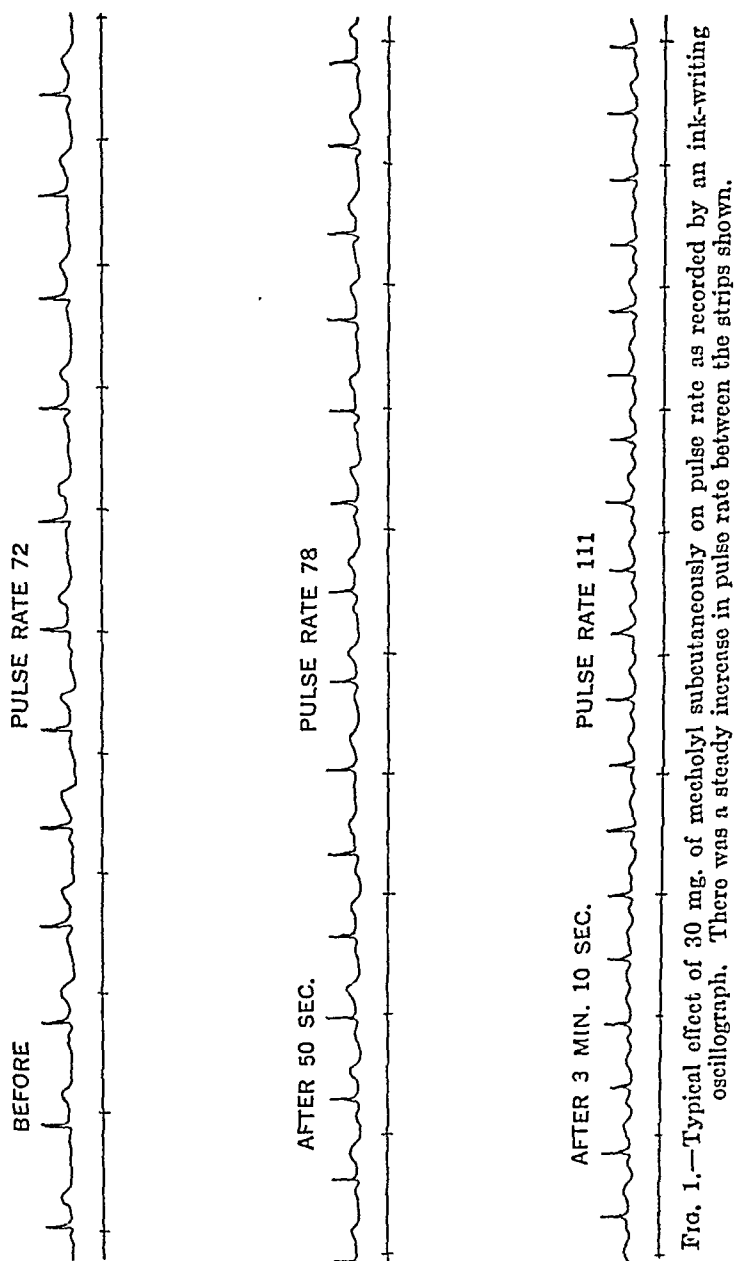


FIG. 1.—Typical effect of 30 mg. of mecholyl subcutaneously on pulse rate as recorded by an ink-writing oscillograph. There was a steady increase in pulse rate between the strips shown.

In the second case, at the height of the amytal narcosis, the blood pressure had fallen 64 mm. of mercury, accompanied by a rise in pulse rate of 10 beats per minute. The injection of 20 mg. of mecholyl caused a still further drop in blood pressure of 18 mm. of mercury and a rise in pulse rate of 16.

In the third case, the injection of sodium amytal resulted in a fall in blood pressure of 14 mm. of mercury and a drop in pulse rate of

TABLE 7.—EFFECT OF SIMULTANEOUS ADMINISTRATION OF ACETYL-BETA-METHYLCHOLINE AND ADRENALIN.

Patient.	Diag.	Control period.		Reaction at height.					Condition at end of test.			Reaction.
		B. P.	Pulse rate.	Mecholyl (mg.).	Adrenalin in cc.	B. P.	Pulse rate.	Time in min.	B. P.	Pulse rate.	Time.	
E. Ba.	D. P.	130/80	68	30 (s. c.)	0.5 (s. c.)	110/60	120	3	124/70	64	26 min.	
E. B.	D. P.	126/80	68	30 (s. c.)	0.5 (s. c.)	80/50	104	4	104/58	80	40 min.	
H. P.	D. P.	100/70	80	30 (s. c.)	0.5 (s. c.)	90/?	112	2	114/80	80	1 hr.	
											16 min.	
A. F.	D. P.	100/60	72	30 (s. c.)	0.3 (i. v.)	144/80	104	1	88?	100	16 min.	Cardiac fibrillation.
C. F.	D. P.	120/80	98	30 (s. c.)	0.3 (i. v.)	140/70	132	2	100?	92	21 min.	
J. B.	D. P.	112/60	68	30 (s. c.)	0.3 (i. v.)	164/50	100	1	108/46	76	16 min.	Pallor distress and cardiac fibrillation.
J. P.	D. P.	118/60	88	30 (s. c.)	0.3 (i. v.)	180/70	112	1	110/58	88	20 min.	
A. McN.	D. P.	114/?	100	30 (s. c.)	0.3 (i. v.)	100/?	170	1	100/?	112	54 min.	

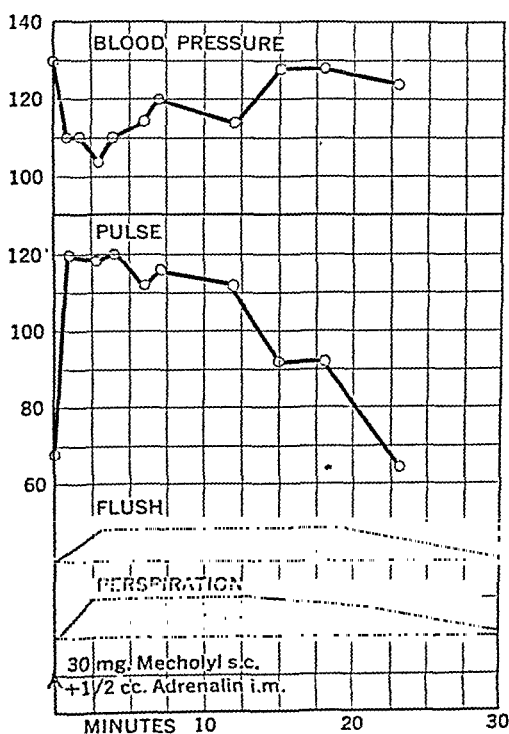


CHART VII (Dementia præcox).—The effect of the simultaneous administration of mecholyl and the intramuscular administration of adrenalin. Note that the adrenalin is unable to prevent the usual drop in blood pressure due to mecholyl. The adrenalin also has no apparent effect on the flushing and secretory responses.

4 beats. Thirty mg. of mecholyl now caused a further drop in blood pressure of 26 mm. of mercury and a rise in pulse rate of 52.

In the fourth case, the blood pressure, following sodium amytal injection, fell 18 mm. of mercury and the pulse rate remained unchanged. Injection of 30 mg. of mecholyl caused a further drop in blood pressure of 10 mm. of mercury and a rise in pulse rate of 20 beats per minute.

Although flushing and increased salivation occurred in each case, perspiration was only slight in 3 of the cases and moderate in the fourth case (Table 6, Chart VI).

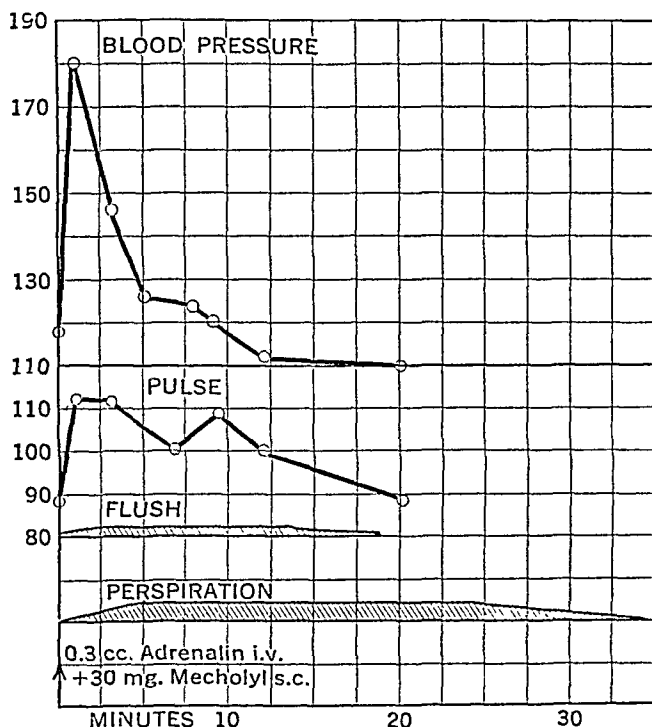


CHART VIII (Dementia præcox).—The effect of the simultaneous administration of mecholyl and the intravenous administration of adrenalin. Here the adrenalin predominates over the mecholyl as regards the blood pressure. The adrenalin also possibly has caused a diminution in the other responses due to the mecholyl.

Combined Effect of Acetyl-beta-methylcholine and Adrenalin. The sympathomimetic and rapid effect of adrenalin would seem to make this drug an ideal antagonist to mecholyl. In 8 dementia præcox subjects, the two drugs were administered simultaneously. The mecholyl was given in 30 mg. doses and by subcutaneous route. In 3 cases the adrenalin was administered subcutaneously in 0.5 cc. doses and in the other cases it was administered intravenously in 0.3 cc. doses. When both drugs were given by subcutaneous route, the effects appeared to be those of mecholyl alone. When the adrenalin was given intravenously, however, a moderate to marked rise in blood pressure occurred except in 1 case. This latter subject, devel-

oped an adrenalin reaction characterized by pallor, distress, and transitory auricular fibrillation. The only other visible effect in this case was slight perspiration. In every other case, however, the usual vasomotor and secretory effects and an increase in pulse rate occurred without apparent modification by the adrenalin.

In another dementia præcox subject 0.5 cc. adrenalin was administered subcutaneously. When the blood pressure had risen 20 mm. of mercury, another dose of 0.3 cc. was given. No further rise in blood pressure occurred. The patient developed marked tremor of the upper part of the body and became pale. Thirty mg. of mecholyl subcutaneously now caused a fall in blood pressure of 40 mm. of mercury within 1 minute, and the patient developed a moderate vasomotor and secretory response. Within 5 minutes the blood pressure returned to its original level.

In the last subject, 30 mg. of mecholyl injected subcutaneously caused a fall in blood pressure of 24 mm. of mercury and an otherwise moderate reaction. The blood pressure then returned to within 6 mm. of its original pressure 2 minutes later. At this point 0.5 cc. of adrenalin subcutaneously caused no essential change in blood pressure. Another injection of 0.5 cc. of adrenalin subcutaneously 11 minutes after the first dose now caused a rise in blood pressure of 16 mm. of mercury. The patient developed an adrenalin reaction characterized by pallor and tremors (Table 7, Charts VII and VIII).

Combined Effect of Acetyl-beta-methylcholine and Benzedrine. In another paper⁷ dealing with the pharmacologic effects of benzedrine and its relationship to the sympathetic nervous system, we have commented at some length on the nature of the effects obtained when mecholyl and benzedrine are administered simultaneously or within a short period of each other. Benzedrine is a sympathomimetic drug with a prolonged blood pressure raising effect. In general, the effects are as follows: (1) When the two drugs are given together, the blood pressure is at first lowered (mecholyl effect), but then becomes elevated to above the original level (benzedrine effect). (2) When the benzedrine is given first and a rise in blood pressure induced, mecholyl will cause a sharp fall in pressure which soon returns, however, to the original high level. (3) When mecholyl is administered first and benzedrine then given, the mecholyl effects are as usual striking; these are followed by the gradually increasing effect of the benzedrine. In all of these experiments, the "explosive" activity of mecholyl was strikingly demonstrated.

Discussion. The reaction of the present group of mental subjects to acetyl-beta-methylcholine is essentially similar to that observed in non-psychotic individuals by Starr, Elsom, Reisinger,¹² Page,⁸ and others. The drug evoked a parasympathetic response, including flushing of the face and upper chest, lacrimation, rhinorrhea, and perspiration, associated with a fall in blood pressure.

The increase in pulse rate which regularly followed the administration of the drug is difficult to explain. Starr, Elsom, and Reisinger,¹² who studied 20 normal individuals, observed an increase in pulse rate almost consistently which, however, was transient and often followed by a secondary slowing. When the drug was given by mouth, a diminished pulse rate was observed. Starr, Elsom and Reisinger attempt to explain the transient increase in pulse rate following subcutaneous injections of mecholyl on the basis of a compensatory mechanism for the sudden drop in blood pressure; for they frequently observed a slowing of the pulse rate before and after the period of diminished blood pressure. In their group of subjects given subcutaneous injections of 20 mg. of mecholyl, 4 showed a decrease in pulse rate of less than 10 beats per minute and none an increase of over 10 beats per minute. Only 2 of their subjects showed a fall in blood pressure of more than 20 mm. of mercury.

We have frequently seen much greater and sudden falls in blood pressure, for example, following intravenous injections of sodium amytal which were followed either by an increase or decrease in pulse rate. Furthermore, the group of subjects given a small (5 mg.) dose of mecholyl showed a definite increase in pulse rate associated usually with an insignificant change in blood pressure. Only 1 of them, however, showed a secondary slowing in pulse rate. These latter experiments seem to prove definitely that the increase in pulse rate following mecholyl administration is not a compensatory response to the blood pressure change. Although the pulse rate increases following either subcutaneous or intravenous administration of mecholyl, the drug has been definitely shown by Comroe and Starr¹ to slow the heart when it is directly applied to the muscle. These authors have also demonstrated that the drug acts as a parasympathetic stimulant on the gastro-intestinal tract, the uterus and bronchi. The ability of the drug to cause vasodilatation has also been demonstrated by Comroe and Starr,¹ Goldsmith² and others. That the cerebral vessels partake in this vasodilatation is indirectly demonstrated by the rise in cerebrospinal fluid pressure, such as occurs following the administration of acetylcholin, histamin and amyl-nitrite.

That atropine is markedly antagonistic to mecholyl has been demonstrated by Hunt,³ Simonart,¹⁰ Comroe and Starr,¹ and others. Hunt,³ from his work on animals states: "The fact that acetyl-beta-methylcholine continues to cause a fall in blood pressure even after very large doses of atropine is one of its most characteristic properties." Simonart¹⁰ also observed a fall in blood pressure in animals following large doses of atropine. In the cases here recorded, however, it is to be noted that mecholyl caused a definite drop in blood pressure after a large dose of atropine in 1 case, while in 2 other cases there was either no fall or a slight fall in blood pressure.

In other cases not here recorded, large intravenous doses of atropine were able to prevent a fall in blood pressure following subcutaneous administration of mecholyl. Our observations further show that preliminary administration of atropine completely inhibits the other effects of mecholyl. When atropine is given following mecholyl, the blood pressure not only returns to, but, in some cases, it may even rise above the original level. This phenomenon was present in 3 of our cases. When the two drugs are simultaneously administered, the blood pressure may remain unchanged, increase, or diminish, depending upon the quantities of the drugs given. If the dose of atropine is moderate or large, the vasomotor and secretory response of the mecholyl is readily inhibited.

When mecholyl is given during sodium amytal narcosis, the effect on the blood pressure is additive, the combined fall in pressure being very great. The visible effects of the mecholyl do not appear to be changed except for a less than the usual degree of perspiration. This diminution in perspiration suggests that the amytal may have some depressing effect on the parasympathetic system.⁶

Mecholyl is still able to cause a fall in blood pressure after a rise induced by adrenalin. Again, preliminary administration of mecholyl prevents a rise in blood pressure when adrenalin is administered. This has been previously shown by Hunt and Renshaw.⁴ When the two drugs are given simultaneously, the resultant blood pressure reaction appears to depend upon the relative dose of each and their modes of administration. Thus, if the adrenalin is given intravenously and the mecholyl subcutaneously, the blood pressure definitely rises. If, however, both drugs are given subcutaneously, the blood pressure falls. Adrenalin, however, is unable to modify the outer manifestations evoked by mecholyl. Benzedrine, because of its slower action, causes but little interference with the mecholyl effect. However, once the latter effect is past, the blood pressure raising effect of benzedrine continues unabated.

Various clinical applications of the pharmacologic effects of mecholyl are suggested. Starr¹¹ has already reported upon the striking effect of the drug in paroxysmal auricular tachycardia and has also suggested its use in auricular flutter and in the occasional very severe case of ventricular extrasystolic arrhythmia. The effects of the drug in increasing the tonus of the gastro-intestinal tract suggest its use in various atonic conditions of the bowel.⁹ We have already begun its use in such conditions and will report upon the results in another communication. The rapid and extreme effect in lowering the blood pressure has naturally suggested its use in hypertension. However, as various authors have already shown, the effects of the drug, when given subcutaneously, are so transitory and its effect by mouth so slight that so far progress in this attractive field has not been made. It is possible that with the use of special preparations of the drug, the answer to the problem may be found.

Summary and Conclusions. In a group of psychotic subjects, including 18 various types of dementia præcox and 2 general paretics, acetyl-beta-methylcholine (mecholyl) was first administered alone and then in combination with atropine, sodium amytal, benzedrine, and adrenalin. The following effects were noted:

1. By subcutaneous route in 30-mg. doses, mecholyl produced flushing of the face and chest, moderate to marked perspiration, salivation, rhinorrhea and lacrimation, a moderate fall in blood pressure, a rise in pulse rate, and a rise in cerebrospinal fluid pressure.

2. By subcutaneous administration in 5-mg. doses, the drug produced a rise in pulse rate sometimes followed by a secondary slowing, usually a slight rise in blood pressure, and a slight degree of flushing of the face. All these effects may be explained on the basis of parasympathetic stimulation, except for the rise in pulse rate. This increase in pulse rate we are unable to explain.

3. No change was noted in the mental reactions or behavior of the subjects.

4. A marked antagonism exists between acetyl-beta-methylcholine and atropine. Atropine quickly overcomes the effects of mecholyl. Not only are the vasomotor and secretory effects of mecholyl quickly checked by atropine, but the blood pressure may return to even a higher than the original level, if the dose of atropine is great enough or given intravenously. Preliminary large doses of atropine prevent the usual marked fall in blood pressure which is produced by mecholyl. When the two drugs are given simultaneously, the effects on the blood pressure appear to depend on their quantitative doses and the routes administered. Whether the atropine is given before or following the mecholyl, the vasomotor and secretory effects are readily prevented or checked.

5. The combined effect of sodium amytal and mecholyl on the blood pressure is additive, the resultant fall in blood pressure being very great. The only observable antagonistic effect of the amytal on the mecholyl reaction is a somewhat diminished perspiration. This suggests that sodium amytal has a possible depressing effect on the parasympathetic nervous system.

6. The effect of the combined administration of adrenalin and mecholyl appears to depend upon their route and the quantities administered. When both are given subcutaneously, the effect of the mecholyl overshadows the adrenalin as regards the blood pressure. When the adrenalin is given intravenously, however, the blood pressure reaction of this drug overshadows that of mecholyl. Adrenalin, however, is unable to check or modify the other visible effects of mecholyl. The same statement holds true with reference to the sympathomimetic drug benzedrine, the prolonged pressor action of which can be temporarily nullified by acetyl-beta-methylcholine.

7. Certain clinical applications of the drug are suggested. Its value as an exceedingly active preparation in the study of various sympathetic-parasympathetic effects is borne out in these experiments.

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IODINE-RESISTANT HYPERTHYROIDISM.

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TWELVE years ago Plummer⁷ definitely established the therapeutic value of iodine in the pre-operative preparation of patients with thyrotoxicosis. There immediately followed ample confirmatory reports.^{2,4,11} These reports were fundamental not only in confirming the original work of Plummer but in depicting the exact nature of the iodine remission. Subsequently, with the generalized acceptance of pre-operative iodization new problems inherent to this particular usage became evident.

The basic writings^{3,11,10,12,13} on this subject early demonstrated that all cases of hyperthyroidism did not show a uniform response to iodine medication. In the classical remission there was a prompt amelioration of all toxic manifestations associated with a marked decrease in the basal metabolic rate. However, in some instances the administration of iodine was associated with little or no clinical improvement and a correspondingly lessened depression in the basal rate. In still other cases there actually appeared to be an intensification of symptoms associated with a rise in metabolism. This latter group subsequently came to be known as cases of "iodine-resistant hyperthyroidism."

The purpose of this study was to try to determine why these cases failed to show the usual response to pre-operative iodization.

Materials and Methods. The basal metabolic rate determinations, before and after the administration of iodine, formed the principal basis for selecting this material. The basal metabolism was chosen because it forms the simplest and most accurate objective data available for compara-

tive study. Only patients with satisfactory metabolic determinations were considered eligible. Cases of recurrent hyperthyroidism or those having had previous surgical intervention, Roentgen ray or radium therapy, or iodine within 3 months before coming under observation, were not included. Borderline cases or those presenting a question in diagnosis were similarly excluded.

For comparative study, each case was classified into 1 of 4 groups. The group designation was determined by the type of metabolic response in the presence of a positive or negative history of previous iodization.

GROUP A. Negative history of previous iodine therapy. No change or a rise in metabolism following pre-operative iodization.

GROUP B. Metabolic response similar to Group A and with a history of iodine medication sometime in the past, but not more than 3 months prior to when first coming under observation.

GROUP C. Negative history of previous iodine therapy. A depression in metabolism of 10% or less after pre-operative iodization.

GROUP D. Metabolic response similar to Group C and with a history of iodine medication sometime in the past, but more than 3 months prior to when first coming under observation.

In classifying these cases it will be noted that patients in Groups B and D had received iodine in the past and in Groups C and D there was some depression in the metabolic rate. A word of explanation will clarify why these apparent exceptions were included. Current opinion dictates that if iodine has been administered to a patient, no amelioration of the toxic manifestations or decrease in metabolism may be anticipated unless a period of abstinence from all iodine therapy be effected before beginning the period of pre-operative iodization. In accordance with this teaching a patient that gave a history of previous medication but had not taken any form of the drug for at least 3 months before coming under observation was considered eligible for this series. The cases with a lowering in metabolism of 10% or less were considered eligible because it was felt that this minor difference may be discounted for mechanical errors in the recording apparatus. Thirty-nine cases fulfilling these requirements were selected for this series.

The method was to study every possible clinical and pathologic manifestation. Special note was given to the age, sex, duration of symptoms, history of previous iodization and physical findings of each patient. Collectively, the reaction during the operation, the immediate postoperative course, the period of hospitalization and the subsequent "follow-up" constituted a major part of this study. Finally the gross and minute pathologic alterations of the thyroid were carefully investigated.

Presentation of Data. *History.* No extraordinary features were noted in the age or sex incidence of these patients. The oldest was 59 years, the youngest 21 (average, 40.2). Twenty-eight (71.7%) were females, 11 (28.2%) were males.

A review of the duration of symptoms appears to be of greater significance. The longest duration was 8 years, the shortest but 2 weeks, giving an average duration of 12.9 months. In this connection it is well to note that in 30 cases (76.9%) symptoms were present for a year or less, giving an average duration of 4.3 months.

In the examination of these patients the objective findings did not differ in any way from the usual findings of other thyrotoxic patients.

Period of Pre-operative Iodization. The pre-operative period included a consideration of the changes in metabolism, pulse, weight and clinical picture. The individual changes for each case are tabulated in Table 1.

TABLE 1.—ANALYSIS OF DATA.

Case	Age.	Sex.	Dur. of symptoms, mos.	Pre-iodine B.M.R.	Period of iodization, days.	Post-iodine B.M.R.	Change in B.M.R.	Change in weight.	Change in pulse.
Group A.									
5145	38	F	0.5	+24	10	+25	+1	-2	0
5633	54	F	1.0	+15	19	+46	+31	-11	
8459	37	F	1.0	+34	22	+35	+1	-2	+2
8632	22	F	1.0	+24	23	+32	+8	+1	+5
6514	50	F	1.5	+25	44	+44	+19	+2	+6
8332	36	F	2.0	+36	37	+45	+9	+23	+8
7519	54	F	2.0	+27	31	+27	0	+4	-6
6089	35	M	2.0	+30	10	+33	+3		
4162	37	F	2.5	+33	28	+35	+2	-3	-22
3774	21	F	3.0	+20	12	+20	0	+24	-30
3599	34	F	4.0	+22	16	+34	+12	-1	-4
5294	26	F	4.0	+59	11	+60	+1	+3	
9300	43	M	6.0	+49	27	+53	+4	+3	-8
4873	..	M	12.0	+30	18	+37	+7	+2	
6840	49	F	12.0	+10	13	+11	+1	+4	+8
6205	37	F	12.0	+16	16	+34	+18	+4	-22
4495	39	F	24.0	+63	11	+70	+7	+1	+10
6417	43	M	24.0	+32	25	+53	+21	+3	+6
4806	50	F	24.0	+35	14	+35	0	+3	-14
8694	35	F	36.0	+35	41	+38	+3	+1	-10
5673	34	F	36.0	+39	18	+54	+15	+2	+8
5849	55	M	60.0	+18	16	+31	+13	+1	+20
Group B.									
3184	38	F	4.0	+37	9	+55	+18	+1	-16
4787	30	M	12.0	+48	11	+51	+3	-1	+4
5886	23	F	24.0	+30	14	+38	+8	0	+3
9155	57	F	48.0	+16	21	+18	+2	+2	-2
Group C.									
4032	39	M	0.75	+54	11	+52	-2		
7803	58	M	1.0	+46	19	+41	-5	+1	+4
4473	29	F	2.0	+52	17	+50	-2	0	+7
7351	36	M	2.0	+45	15	+42	-3	+5	-11
8089	42	F	2.0	+40	27	+36	-4	+2	+1
7454	28	F	2.0	+26	14	+25	-1	-2	-2
8502	30	F	2.0	+52	45	+51	-1	+5	-23
5466	55	F	2.5	+55	41	+51	-4		
2612	32	M	6.0	+55	19	+54	-1	0	+2
3946	59	F	6.0	+37	9	+36	-1	+7	
6243	49	F	96.0	+34	19	+31	-3	+3	+4
Group D.									
6022	40	F	12.0	+57	25	+52	-5	+2	-40
5642	55	M	9.0	+18	12	+17	-1	+4	-8
Average	40.2	..	12.9	+35.3	20.2	+39.7	+4.4	+2.5	-3.7

In referring to Table 1 it will be noted that there are 6 cases with basal metabolic readings ranging from +10 to 20. Since the toxicity of patients having relatively low basal metabolic rates is always questioned, a supplementary survey of these cases will not be amiss. Subjectively, all 6 patients complained of nervousness. In 2 there was an associated irritability and in a third marked emotional instability was in evidence. Five of the 6 had lost an average of 12.9 pounds in weight. The same number complained of tachycardia with heart consciousness. Objectively the pre-iodine basal pulse rate was definitely increased. The maximal rate was 154, the minimal 87, or an average of 115. Exophthalmus and asso-

ciated eye signs were present in 2 cases. Auricular fibrillation was present in 2. In 5 there was a tremor of the extended fingers. Definite thyroid enlargement with an audible bruit was present in 5 of these 6 patients. In each instance histologic study of the surgically removed specimens revealed evidence of hyperplasia. Finally in all 6 patients definite clinical improvement was effected by surgical intervention. Thus, notwithstanding the relatively low basal metabolic rates of these cases, it is felt that with such unmistakable evidence their inclusion in this series is warranted.

The average changes in metabolism, basal pulse and weight for each group are graphically illustrated in Charts I, II and III.

In 22 instances there were definite statements relative to the subjective changes experienced following pre-operative iodine therapy: 18 (81%) experienced definite improvement; in 3 cases (13%) no change was noted; 1 patient (4%) felt that her condition was aggravated by the therapeutic administration of iodine.

Response to Surgery. The response to surgery included a consideration of the reaction to operative manipulation, the immediate postoperative course for 24 hours with the subsequent period of hospitalization and the period of "follow-up" study.

In this series there did not occur a single operative death. In 1 patient the postoperative course was alarming for the first few days, the pulse rate at times reaching 180. There then followed progressive improvement until the tenth postoperative day, when the patient was discharged with a pulse rate of 80. In 6 cases there occurred mild postoperative reactions manifested by an average rise in the pulse rate to 135 with an average increase in temperature to 101.3° F. In each instance there was a gradual decline to normal over a period of a few days.

The subsequent "follow-up" was of importance in eliciting such factors as residual thyrotoxicosis, recurrent hyperthyroidism and persistent hypothyroidism. The longest period of postoperative observation was 6 years and 8 months in 2 cases. The shortest period was 2 months in 2 patients operated upon this year, an average of 27.2 months.

There have been no cases of recurrent or residual thyrotoxicosis in this series. Six patients (16%) have been mildly hypothyroid at the end of an average of 23.3 months. The last average basal rate was -17 while taking an average of 1 gr. of desiccated thyroid daily. In the remaining 31 cases (82%) there was no evidence of hypothyroidism at the end of an average of 27.3 months.

Pathologic Changes. The pathologic alterations observed in these glands appear to be of greater significance than any of the foregoing considerations. It is advisable at this time to preface the presentation of these data by saying that the pathologic alterations observed in this study are presented only in general terms, since a detailed consideration is being reserved for a subsequent communication.

Satisfactory data on the macroscopic findings were available in every case. However, since it is felt that the so-called exophthalmic goiter and toxic adenoma are but variations of a single morbid disease, no attempt has been made to make a gross anatomic differentiation. It obviously follows then, that of the various pathologic manifestations the microscopic alterations would constitute the principal part of the pathologic survey. Histologic sections suitable for study were available for 35 of the cases. For the purposes of comparison an equal number of sections were chosen from patients having had a classical remission following pre-operative iodization. Fig. 1, chosen from the control group, illustrates the complete type of involution effected by iodine.

The most striking feature in the review of these sections was the almost uniform presence of a persistent or residual hyperplasia. Two general types of hyperplasia predominated in these sections. In one the moderate-sized acini presented papillary infoldings of columnar epithelium with a relatively poorly stained colloid (Figs. 2 and 3). The quantitative and qualitative degree of hyperplasia varied from case to case. In some sections many acini were so completely filled with papillary projections that there remained but little or no lumen. Paralleling this extreme epithelial hyperplasia there was either no colloid or only a small amount of poorly stained secretion. In the less hyperplastic sections there was in evidence only small mounds or buds of columnar epithelium abutting an inadequately stained colloid. One degree or another of these changes was demonstrable in 12 cases (34%).

The other type was in part characterized by its focal distribution. In most instances this focal hyperplasia was localized near the periphery of the lobule-like structures. The acini were small, round and lined with a columnar epithelium. In many acini the epithelium occupied so much space that there remained but a small lumen. Paralleling this epithelial hyperplasia there was no secretion or but very little of a poorly stained colloid. Varying degrees of this type was demonstrable in 11 cases (31%). In 2 instances (5%) a mixed type or combination of these hyperplastic forms was in evidence.

In the sections unaccounted for there was still another form of hyperplasia. It is difficult to say whether this was a third type or merely represented a more completely involuted stage of one of the foregoing. In this group the acini were of moderate size, filled with a poor to well-stained colloid and lined with a cubical to columnar epithelium. This form was present in 7 cases (20%).

In one instance (2%) there appeared focal hyperplastic areas made up of compact cords of columnar cells and devoid of any lumen or colloid. In 2 cases (5%) there was wanting evidence of any hyperplasia.

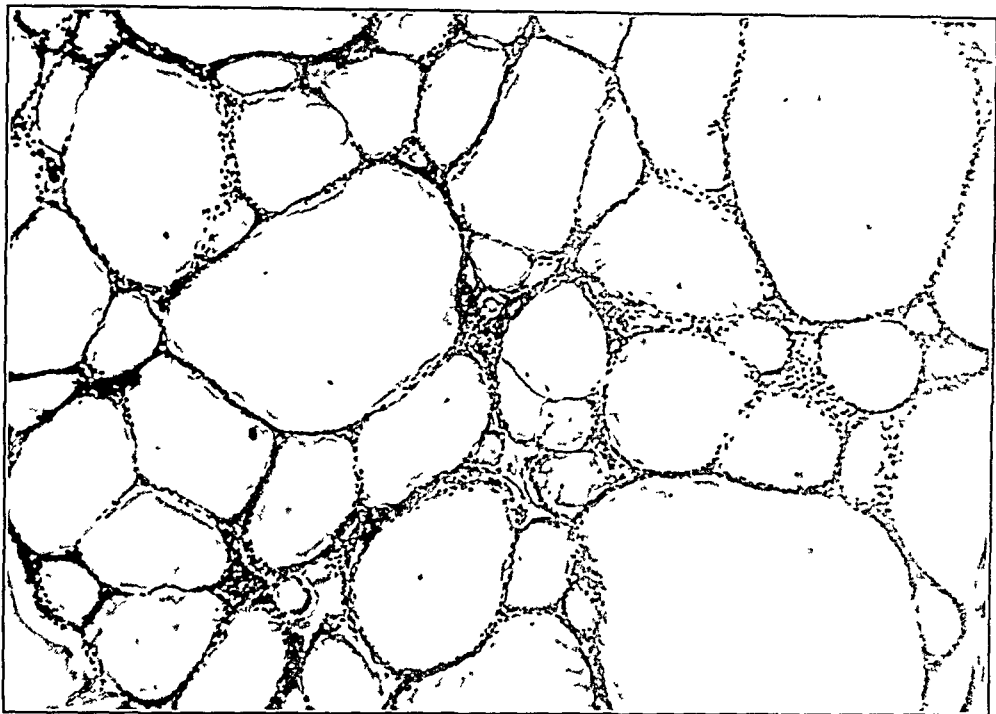


FIG. 1.—Section illustrates complete involution of thyroid induced by iodine. The acini are uniformly distended with a well stained colloid and lined with a flat endothelial-like epithelium. (Mag. $\times 90$, Hem. Eosin.)

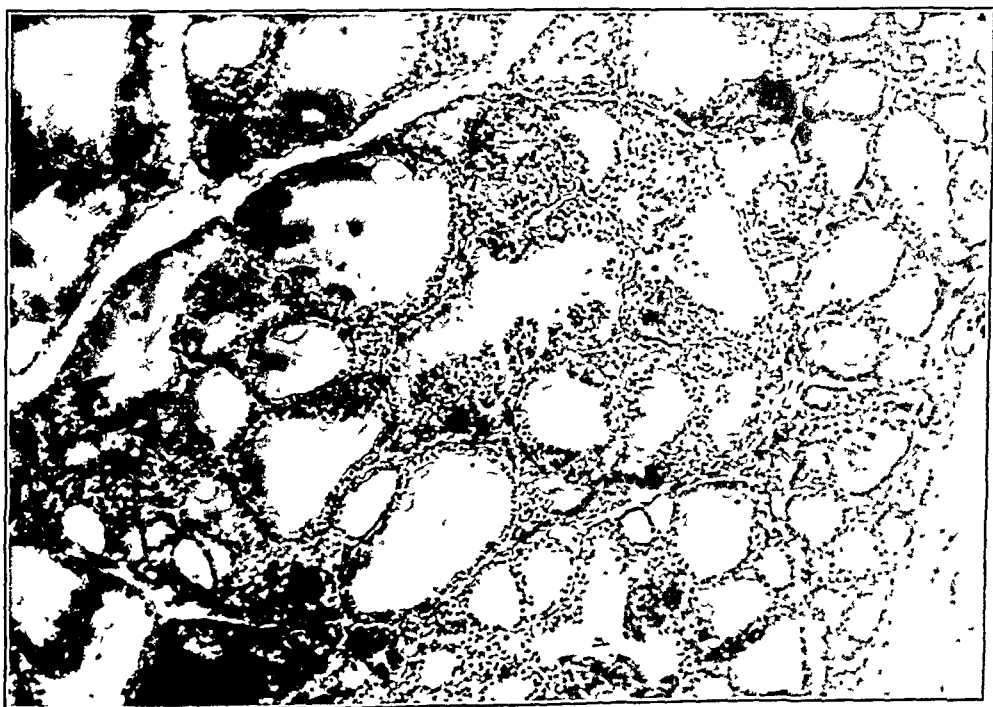


FIG. 2.—Section illustrates incompletely involuted thyroid with moderate-sized acini lined with columnar epithelium and containing a relatively poorly stained colloid. Acinus in the center of the field illustrates papillary infoldings of columnar epithelium. (Mag. $\times 90$, Hem. Eosin.)

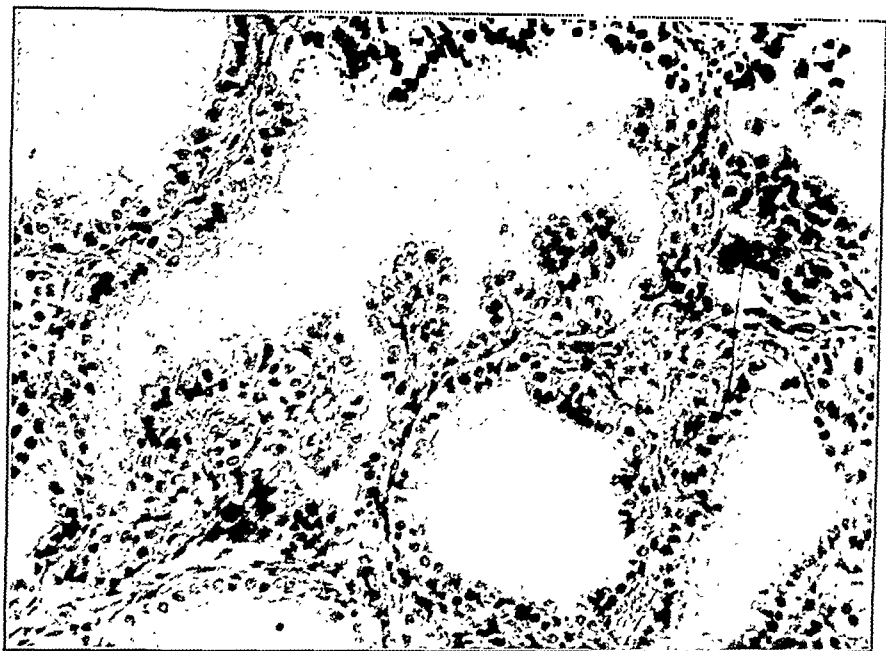


FIG. 3.—Hematoxylin and eosin stained section of hyperplastic thyroid. Greater magnification of Fig. 2 to illustrate papillary infoldings of columnar epithelium. (Mag. $\times 320$.)

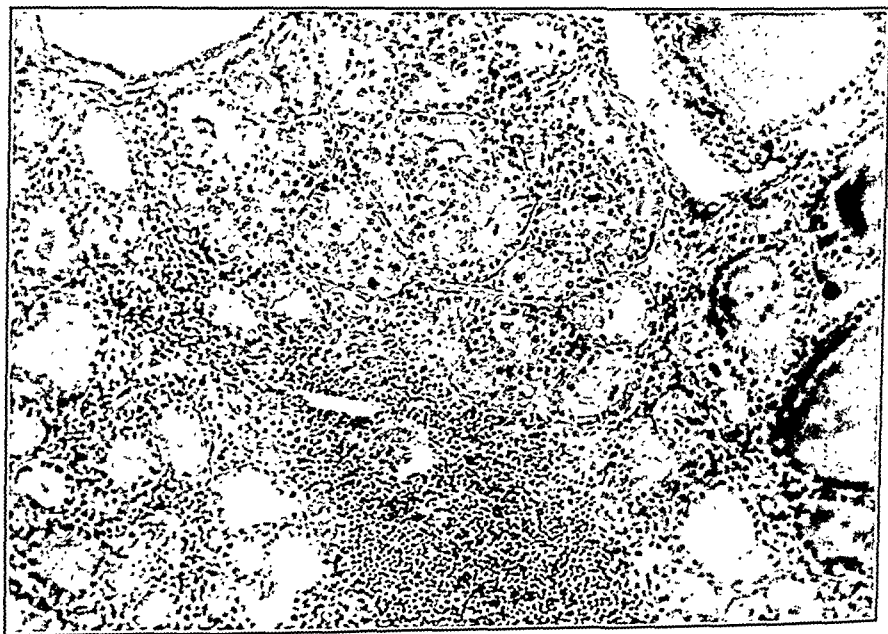
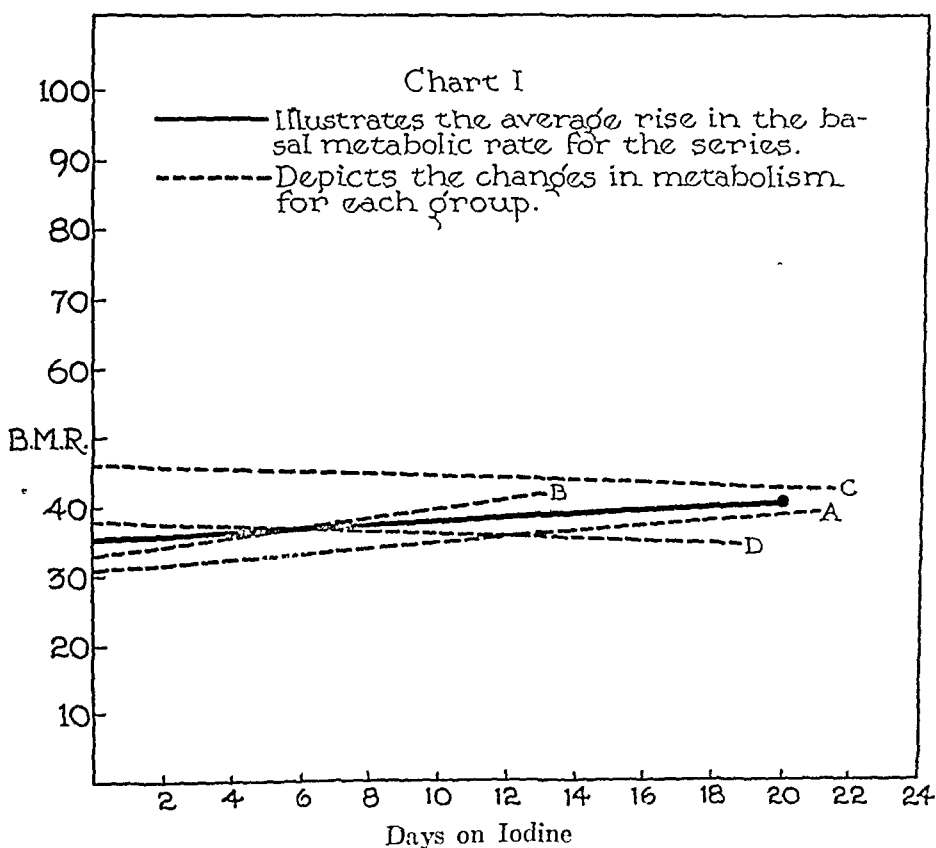


FIG. 4.—Section illustrates second type of hyperplastic thyroid. Focal aggregation of small acini lined with columnar epithelium and containing little or no colloid material. (Mag. $\times 90$, Hem. Eosin.)

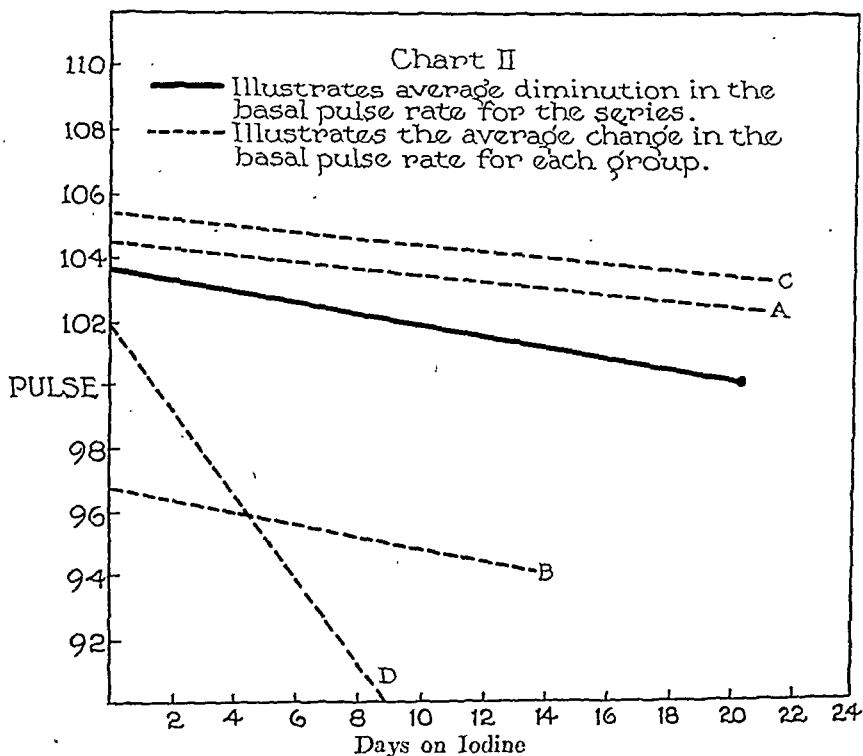
Discussion. The tenor of almost all communications on the iodine-resistant thyroid has been to sound a word of warning in the control and management of these patients. To interfere surgically in the presence of a rising metabolism meant to court disaster. Toward obviating such unfortunate results many suggestions have been offered. Greatly increasing the accepted dosage of iodine has been proposed as a method for the satisfactory control and management of the iodine-resistant thyroid.⁵ Omitting all iodine for some time had as its premise an increased margin of safety in the remission following subsequent iodization.^{2,4} Fractional operations as the safest method for removal of the iodine-resistant thyroid has its adherents.⁸



Such differences of opinion can only mean a lack of understanding fundamentals and consequently inadequate approach to the problem. Though much ado has been made over the iodine-resistant thyroid, it is strange that careful studies of series of iodine-resistant cases should still be wanting in the literature. Impressions have been created and subsequently carried as teachings from only occasional references to a few iodine-resistant cases. These incidental citations have usually appeared during the treatment of some other

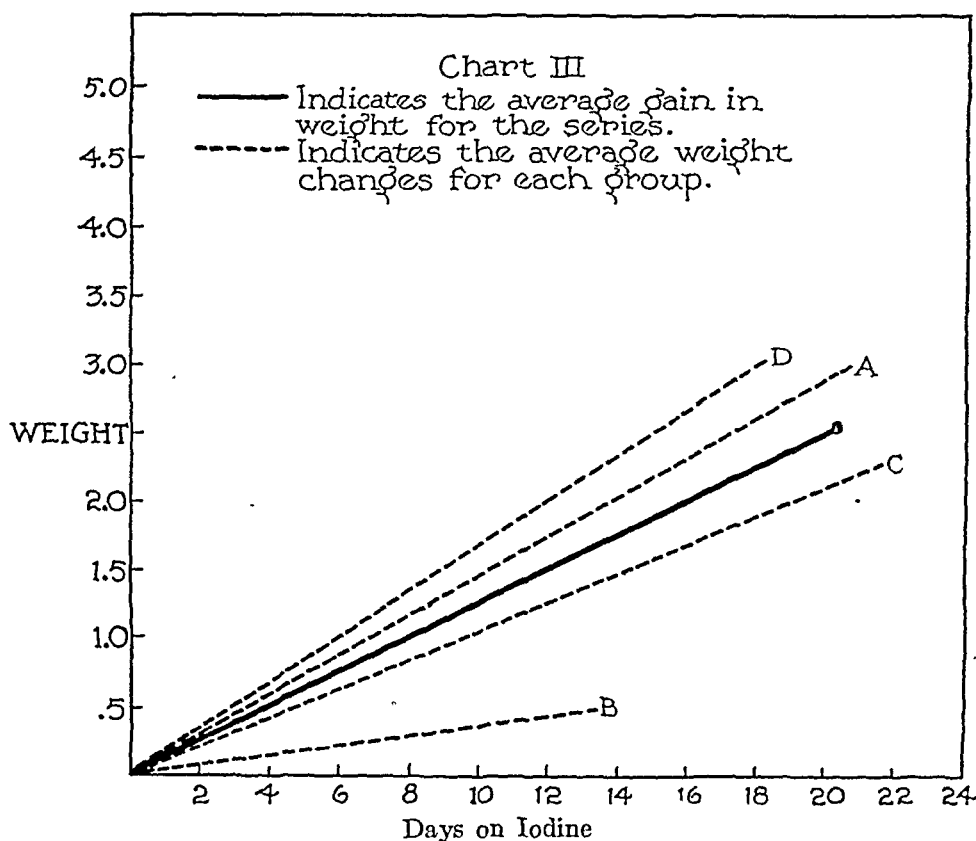
problem inherent to thyrotoxicosis. As a result the basic fundamentals and statistical figures still await their appearance in the literature.

In the foregoing pages the material comprising this study was presented in regular sequence. The first outstanding characteristic was the relatively short duration of symptoms. Potter and Morris⁵ in their study made similar observations. In their series the average duration of symptoms in the iodine-resistant groups was less than in the groups showing satisfactory responses to iodine. These writers felt that the iodine-resistant state may be due in



part to the long-continued ingestion of iodine and consequently anticipated that symptoms might be present for a longer period in these cases. From evidence adduced in this study it appears that the previous ingestion of iodine is not instrumental in effecting the iodine-resistant state. In attempting to correlate this relatively short duration of symptoms a more logical interpretation may be found in the contention of Means.^{6a} This writer believes that the iodine-resistant state may be explained on the basis that the medication is given at a time when the disease is rapidly increasing in severity and that the effect of the iodine is merely to hold the status constant.

Following the relatively short duration of symptoms the next principal feature is the pre-operative period of iodization. The changes in metabolism as set forth in Table 1 and Chart I are self-explanatory. Closely associated with these changes in metabolism are the changes in the pulse, weight and clinical picture. Chart I depicts an average rise in metabolism of 4.4%. Taken alone this would suggest an intensification of the existing thyrotoxicosis. However, notwithstanding this average rise in metabolism, it will be noted that there was an associated depression of 3.7 beats per minute in the average pulse rate (Chart II) and an average weight



gain of 2.5 pounds (Chart III). Further, 81% of these patients experienced definite clinical improvement. Although these changes are not as striking as noted in the cases making an average response to pre-operative medication,¹ they suggest that despite the ascension in metabolism these patients are in a measure definitely improved by pre-operative iodization.

The immediate response of these patients to surgical intervention is reflected in the relatively mild postoperative course and to the fact that there did not occur a single operative fatality in this series. These results are in a great measure ascribed to the radical one-stage operation described by Richter.^{a, b, c}

These results, however, are only in partial agreement with other writings on the iodine-resistant thyroid. Potter and Morris⁸ in their study classified their material into 3 groups. In the exophthalmic group no mention was made of the operative mortality. In the adenomatous group (10 cases) and colloid group (2 cases) operative fatalities were wanting. In striking contrast, however, Means^{6a} has given 27.3% as the operative mortality for the iodine-resistant thyroid. This apparent discrepancy may be explained by two factors: (1) The iodine-resistant group referred to by Means was a small one, consisting of 25 cases with 6 deaths; (2) in the experience of this writer the cases "that fail to respond to iodine are likely to be older and more likely to have heart disease."^{6b}

To help clarify this apparent discrepancy the writer has carefully reviewed, for additional evidence, the last 1500 consecutive thyroidectomies on the services of Dr. Richter. This series included only thyroidectomies for primary, secondary and recurrent hyperthyroidism. There were 9 operative deaths (0.6%). Further, the 9 fatalities were carefully studied and in each case there was wanting evidence of the iodine-resistant state.

The "follow-up" period further aided the evaluation of surgical interference. In 16% there was a persistent mild hypothyroidism and in 82% there was no hypothyroidism at the end of 23.3 and 27.3 months, respectively. These figures are in accordance with similar observations made in large series of cases having an average response to iodine.

The pathologic alterations encountered in this series was impressive and important to this study. The outstanding feature was the uniform presence of persistently hyperplastic areas. On the basis of these findings there is readily offered a tangible explanation for many of the unusual clinical phenomena. It must be conceded that persistent focal areas of hyperplasia distributed throughout the gland may be sufficient to elevate or maintain a constant basal metabolic rate. On the other hand, that some improvement does occur following iodization can be reconciled in that the gland does undergo partial involution and hence the degree of preternatural activity is reduced but not completely controlled. What appears to be of greater importance is that a complete uniform involution does not always follow iodization. Why there should persist focal areas of hyperplasia that have resisted the involution produced by iodine can at this time be only a matter of conjecture.

Summary. 1. The age and sex incidence, clinical manifestations and physical findings of the iodine-resistant thyroid patient do not differ from similar findings in the average patient with thyrotoxicosis.

2. The duration of symptoms in this series was less than that usually encountered in the average case of thyrotoxicosis.

3. Notwithstanding the average increase in metabolism, these patients were in a measure clinically improved by pre-operative

iodization. Objectively this was manifest in the decrease of the average pulse rate and the average gain in weight. Subjective evidence of improvement was attested in 81% of these patients.

4. The relatively mild postoperative course and the low operative mortality suggests that satisfactory results may be anticipated following adequate surgical intervention of the iodine-resistant thyroid.

5. There were no recurrences or instances of residual hyperthyroidism in this series.

6. The uniform presence of persistent or residual thyroid hyperplasia offers a tangible explanation for the iodine-resistant state.

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STUDY OF THE OSSEOUS REMAINS OF A PRIMITIVE RACE WHO ONCE INHABITED THE SHELTERS OF THE BLUFFS OF THE OZARK MOUNTAINS.*

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AT some time in the past, the shelters in the bluffs of the Ozark Mountains of Arkansas and Missouri were inhabited by a small-sized people who had moderately long heads. There is no positive means of establishing a definite chronology for the period of their occupation, but judging from the absence of celts, pipes, and bows and arrows, one is lead to suspect that these people lived in very ancient times. They grew such crops as corn, squash, pumpkins, gourds, sunflowers, pigweeds, lambs-quarter and beans. Their food supply was supplemented by native seeds, acorns, fruit of the sumac,² dried fruits and nuts of the region. Fish, birds and mammals were added to their diet by means of bony fish hooks, nets,

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snare and atl-atl darts. Their funeral customs furnish the only positive information concerning them. For disposal after death, the bodies were flexed to a knee-chest position (Fig. 1), placed in a feather-down bag, and cached in nests of grass. There is some evidence that all bodies were not flexed and hidden after death. However, so many of the shelters of the bluffs had been "worked" over by representatives of out-of-state museums and by those seeking buried treasures that definite statements cannot be made. Many of the remains that were wanted were taken and chaos was the result.

■ The object of this study was to determine whether there were pathologic changes in the bones of these ancient people which could be translated into terms of present-day clinical entities. If osseous changes were present, we also hoped to determine whether they could be attributed to diseases with which we are unfamiliar at



FIG. 1.—Skeleton in place showing flexion of arms and legs, and long head.

the present time, or to the primitive mode of living or environment of these people. In none of the caches were there any materials, implements or gadgets which would indicate that these people ever had had any contact with European culture; therefore, the presence of osseous changes indicative of syphilis would be of paramount academic interest. Such findings would indicate that syphilis had been endemic among these ancient and now extinct people centuries before Europeans reached the eastern shores of this country.

The material for study, which was obtained from the Museum of the University of Arkansas, was collected under the direction of one of us (S.C.D.). It consisted of the whole or part of an indefinite number of (more than 200) remains and effects as they had been exhumed. The human osseous material from each cache was examined and those parts which showed gross abnormal antemortem changes were retained for this study.

A detailed study of the entire skeleton could not always be made in cases in which a part of the skeleton showed gross pathologic changes. In addition to the plundering of these caches, which already has been mentioned, other destructive forces had been at work during the many centuries since the bodies were hidden away. Not the least among these destructive forces were cave rats, which not only had started focuses for future mortification and decay by their gnawing, but also had removed some of the parts. Fire often has burned some skeletons beyond recognition. The bones of the hands, feet, vertebræ and ribs, which were not in the intact funeral bags, usually were widely dispersed and impossible to find. The patellæ were numerous and, as a rule, were well preserved. Their only abnormality was hypertrophic changes. Pelvic bones outside the funeral bags usually were too incomplete to be reassembled. Not a single rib showed evidence of any abnormal changes such as rickets, infection, fracture or malignancy.

The skulls were dolichocephalic and stenocephalic in shape. There was no evidence that this contour of the skull was the result of disease associated with premature or delayed ossification of the cranial sutures. This shape of head was for the most part racial, and may have been enhanced by sleeping in a semirecumbent position.

There were two craniums with persistent frontal sutures. The persistence of these sutures was not the result of disease.

Mace injuries were common. The skull of a middle-aged man revealed a fracture which extended from the parietal boss on the right side across the vertex of the skull into the left parietal bone. The edges of the fracture were smooth and the fracture had not shattered the inner or outer plates.

Remains of a woman and two children, who had been cached in the same bag, revealed antemortem fractures of the skulls of both of the children. The fracture of the head of the older child, who was about 4 years of age, can be described definitely. Beginning at the vertex of the head and extending laterally through the parietal bones and into the sphenoid bone was an irregular fracture with shattered edges. Inside the cranium were pieces of the shattered bones from the vertex of the skull. The bones of the head of the younger child had been crushed. The bones of the woman were normal. In her pelvis were the bones of a fetus. The fracture of these skulls had been the result of severe blows, and one would suspect that they had been delivered with homicidal intent. Neither the cranial bones nor the long bones of any of these children showed evidence of rickets or deficiency diseases.

A roentgenogram of another adult skull revealed that the nasal accessory sinuses were poorly developed. The floors of the antra were thickened. In one skull there was an increase in the density of the bony lining of the mastoid cells, which was the result of a mastoiditis. In another specimen, there was a rounded region

of rarefaction, which involved only the external table of the skull over and medially to the right occipital bone. The cause of the changes in this skull does not admit of interpretation.

There were several healed fractures (Fig. 2) of the bones of the arms and spinal columns. All the segments were in good position. That these people used splints in the treatment of fractures is a known fact. A rural physician found a mummy which had a fractured right ulna, and around the forearm was a rather neat splint which had been made of reeds and grass cordage. The specimen had been handled by careless hands so many times that it was impossible to ascertain much in the way of details as to the possible effectiveness of its application. The materials were such that an adequate splint, which was light in weight, could have been designed with them. There were two very good examples of a compression fracture of a lumbar vertebra which had healed. Because of the conditions under which these people lived, it is practically inconceivable that these men could have existed as long as they did, if there had been any degree of paralysis.

The state of preservation of the tibiae was very good. This was especially true of those tibiae which revealed increased density. These tibiae were of the greatest interest in the present study; they showed rather marked deformity of the anterior aspects of the middle, proximal and distal thirds of the shafts (Fig. 3). In other words, the subcutaneous surface of the bone was the site of the changes. The deformity consisted of a rounded anterior or cortical surface, which occasionally gave the impression that the bone was bowed anteriorly. In those cases in which the changes had involved the greater part of the bone, there were also changes on the posterior aspects. The rounding of the surfaces apparently was the result of the formation of new bone.

In the bones which revealed advanced changes, the rounded surfaces were hard and rather smooth until one reached the margins of the changes, where there were fine perforations and grooves. The weight of each bone varied and was directly proportionate to the amount of the bone involved. If only a small region in the middle third of the shaft was involved, the bone was not appreciably increased in weight; however, if two-thirds or more of the anterior surface was affected, the density and weight were greatly increased.

The foregoing description of tibiae suggests that the lesions present were the result of a syphilitic osteitis. In an early period of the study it was thought that this was the case; however, two findings rendered such an idea untenable. Aside from the tibial changes, it was found that the rest of the skeletons were normal. There often was a great disparity between the degree of changes present in the two tibiae of the same person, or one tibia frequently was found to be normal. Therefore, some other explanation was necessary to account for these tibial changes. A possible explanation is found in the fact that the tibiae of persons who lived in these

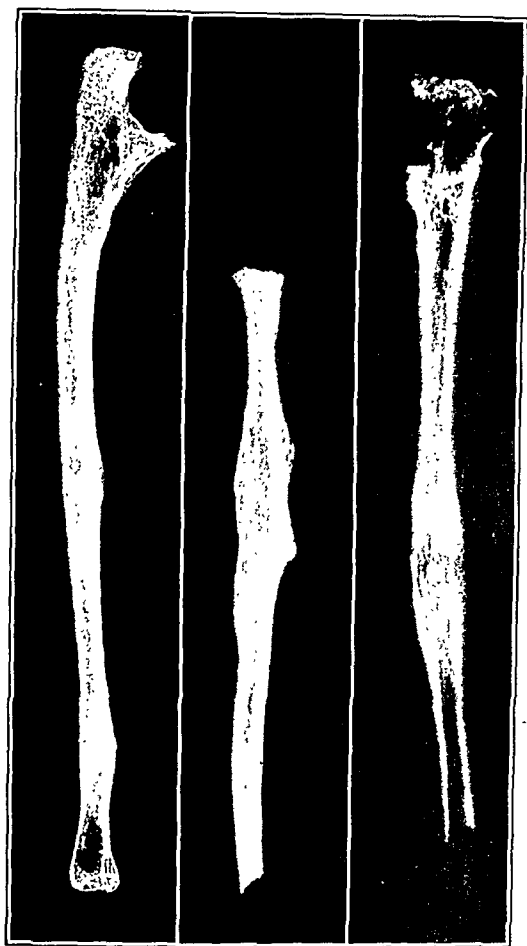


FIG. 2

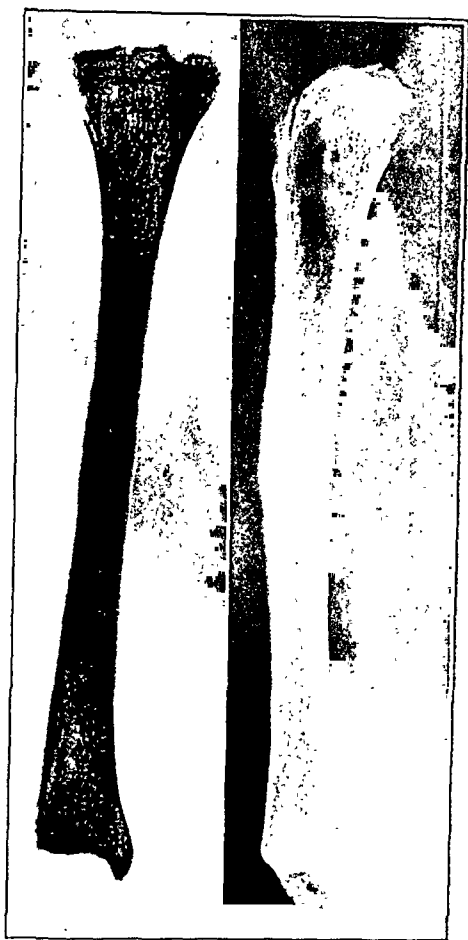


FIG. 3

FIG. 2.—Roentgenogram of healed fractures of bones of the arm.

FIG. 3.—Roentgenogram of tibia showing osteitis of middle third (probably post-traumatic).

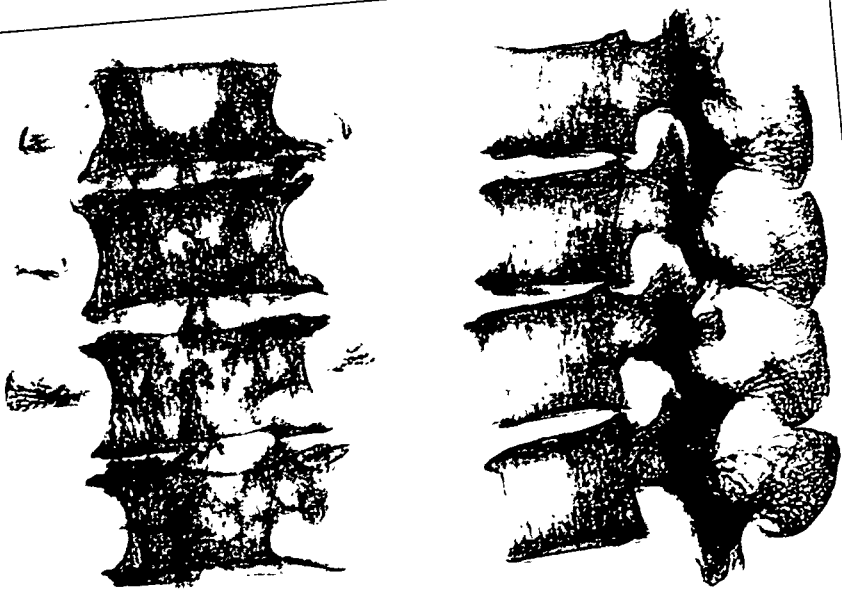


FIG. 4



A



B

FIG. 5

rocky shelters were subjected to considerable trauma by being bumped against boulders on the floors and at the entrances of the caves. A further study of osseous material revealed that some of the tibiae which revealed changes suggestive of syphilis were obtained from caches which probably belonged to a "top layer culture;" that is, they belonged to people who lived in these rocky shelters after the passing of the "Bluff Dwellers" some 20 or 30 centuries ago.

It seems that throughout the ages whenever human osseous remains have been found, the fringes of the articular surfaces are the site of so-called hypertrophic changes which we now associate with senescence. In climates which are subject to extreme changes in temperature and humidity, hypertrophic arthritis is thought to be more prevalent than it is in other climates. Among those whose occupations require physical strain while they are exposed to inclement weather, the disease may be more incapacitating than it is among individuals who are not exposed in this manner. These ancient Americans who lived in the shelters of the bluffs of the Ozark Mountains, where during the winter and spring there is a heavy rainfall and a constantly high humidity, would be expected to be afflicted frequently with this disease. Our study bore out this expectation in every detail. Practically every lumbar vertebra of those individuals who were 30 or more years of age showed evidence of hypertrophic changes (Fig. 4).

In contrast to the frequent occurrence of hypertrophic arthritis of the spinal column, there was no evidence of the deforming disease which is now known as chronic infectious arthritis. There was not a single large joint or small joint of the hands or feet that showed evidence of articular changes which are characteristic of this disease.

Apropos of the absence of evidence of infectious arthritis in the joints is the fact that there was evidence of other infections, such as abscesses of the teeth. There also was evidence of infection of the accessory nasal sinuses and mastoid cells. In other words, these people were susceptible to the common infections of the teeth and sinuses which are recognized at the present time, yet there was not any evidence of the crippling, disabling disease which is known as chronic infectious arthritis.

We selected some mandibles which illustrate that these people must have suffered from toothache, and in some cases there is evidence that they knew that extraction of the teeth was beneficial. The mandible of an elderly person (Fig. 5, *A*) disclosed that the molars had been removed antemortem.

LEGENDS FOR FIGS. 4 AND 5

FIG. 4.—Roentgenogram of lumbar vertebrae showing hypertrophic changes about their borders.

FIG. 5.—*A*, Roentgenogram of mandible healed after extraction of teeth; *B*, evidence of extraction of lower molar teeth, and osteitis.

We believe that another mandible (Fig. 5, B) discloses how the extractions may have been performed. There was a fracture or bursting away of the outer part of the alveolar border opposite where the second and third molars had been removed traumatically. The teeth apparently had been knocked out of the mouth. The proximity of disease suggests that this was not accidental. As a rule, the teeth which were still present were well formed and uniformly good. The latter statement is not intended to convey the idea that this race possesses uniformly good teeth. Carious and decayed teeth tend to fall from the dried specimens with the least provocation and unless there was a considerable amount of infection around the socket one cannot make any statement in regard to a tooth that once occupied an empty socket.

Comment. In 1924, Harrington¹ reported the results of a study of the ancient inhabitants of the rocky shelters of the Ozark Plateau. However, the credit for the discovery of habiliments of the ancient race who inhabited the Ozark district belongs to some unknown members of the Confederate Army who went to the rocky shelters to remove bat guano to manufacture gunpowder.

We do not know how long it has been since this race occupied the Ozark Plateau. There are so many points of similarity between these people and the "Basket Makers" of the southwestern part of the United States, who are known to have lived 2000 or more years ago, that it is fairly safe to estimate that the osseous material which forms the basis of this report is at least 20 centuries old.

Summary. Remains of more than 200 prehistoric bluff dwellers in the Ozark Mountains have been examined for pathologic changes. The outstanding congenital anomalies consisted of two craniums with persistent frontal sutures. Ordinary, present-day types of long-standing infection of the maxillary sinuses and mastoid cells were not unusual. In one specimen there was evidence of a suppurative mastoiditis with drainage to the outside. Mace injuries of the skull were present among adults and children. Several tibiae showed evidence of an osteitis which resembled that caused by syphilis, but there was not sufficient evidence of syphilis in the rest of the skeletons in which these tibial changes were found to warrant a diagnosis of syphilis. These changes in the tibiae could have been the result of trauma incident to the place and mode of living. Hypertrophic changes about the margins of the lumbar vertebrae and occasionally about the knee joints were common among the remains of individuals who were 30 or more years of age. Fractures of the bones of the arm and spinal column occasionally were observed. Dental infections and suppurations were common. The surgical accomplishments of this race at least included the removal of teeth and the reduction of fractures.

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ATROPHIC ARTHRITIS AMONG THE PIMA INDIANS OF ARIZONA.

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It has been more or less generally accepted that atrophic arthritis is practically unknown among natives of the Southwest.^{1,2} It was therefore with interest that a case of this disease in the Pima Reservation Hospital at Sacaton, Arizona, came to the attention of one of the authors. In view of the fact that we were unable to find, in the literature, any reports of atrophic arthritis or any adequate survey of rheumatic conditions occurring among these Indians, the authors decided to make a survey of diseases of the joints present in the Pima tribe.

The Pima Indians, representing approximately 13% of the Indian population of the state of Arizona, have lived for at least 250 years in the same locality along the Gila and Salt River beds in the heart of the Southwest "desert" country. They are essentially a healthy, prospering, agricultural people, at present slightly increasing in numbers. The headquarters of the government agency is located at Sacaton, Arizona (altitude 1274 feet), about 40 miles southwest of Phoenix and 80 miles northeast of Tucson. The climate is typical of the Southwest, and closely resembles that of Phoenix, which has a mean temperature of 69.7° F., a rainfall of 7.59 inches, and a relative humidity of 56% at 6 A.M., 28% at noon, and 28% at 6 P.M. These are mean yearly averages for a period of 36 years.³ A striking feature of the climate is the wide diurnal variation in temperature. There are living on the Reservation, at present, 5745 Pima Indians of whom, it is estimated, about 2700 are adults. We felt that this would be an ideal group for study.

There is an adequate medical service on the Reservation. This consists of a 28-bed hospital under the supervision of a resident doctor and a staff of 4 graduate nurses. A dispensary is associated with the hospital and in addition there are 3 other dispensaries on the Reservation, each with an attending physician. These last have a total of 4 field nurses serving them. The entire medical service functions as a unified whole under the direction of the hospital. No cases of tuberculous joint disease are included in this survey as cases of tuberculosis in any form are removed from the Reservation to a sanatorium as soon as diagnosed.

In making this survey all cases of chronic joint disease known to the medical staff of the Reservation were investigated, and further,

through government field workers, inquiries were made about persons suffering from disabilities of the extremities. We personally saw each case in these two groups and made the following diagnoses:

*Atrophic arthritis	3
*Spondylitis with polyarthritis	1
Monoarthritis (possibly gonococcal)	1
Osteomyelitis of the elbow and os calcis	1
Hemiplegia with residual paralysis	1

* Cases discussed in this paper.

It may be mentioned that during the winter of 1935-1936, 2 young Indians were treated for "acute articular rheumatism," and further, at the time this survey was made there was, under treatment in the hospital, a child with Sydenham's chorea complicated by a unilateral pleural effusion.

Of the 3 cases of atrophic arthritis, 2 occurred in Indians who had lived all their lives on this Reservation. Case reports of the latter follows:

Case Abstracts. CASE 1.—(Fig. 1). A. G., a full-blooded female Pima Indian, aged 42, was seen by us in the hospital. She had been well until 4 years ago when she noticed pain and swelling of her ankles. This became progressively worse until 2 years ago when her hands and wrists also became involved. A Roentgen ray photograph of one of her hands then showed definite joint lesions. Her tonsils and some abscessed teeth were removed following which the pain in her ankles became less severe. Her hands and wrists did not improve. One year ago her elbows became involved, with pain and swelling. She states that her symptoms have been less severe in hot weather.

The patient's family history is non-contributory. She has been married 26 years. Her husband is living and well and she has 5 living children. She had a spontaneous abortion 3 years ago and her menopause occurred 1 year ago. The only childhood disease that she can recall is whooping cough. She has never had any leucorrhea or symptoms referable to the genitourinary tract.

Physical examination revealed a well-nourished middle-aged Indian woman, 5 feet tall, weighing 143 pounds and of moderate intelligence. The findings were normal except for the extremities and a slightly elevated blood-pressure (158/90). Several teeth were missing. The tonsils had been cleanly removed and the mucous membrane appeared normal. The lungs were clear. The heart was not enlarged to percussion. There were no murmurs. The radial pulse was soft and compressible. The abdomen appeared normal in all respects. Pelvic examination revealed no abnormalities. The reflexes were normal.

There was bilateral fusiform swelling of the proximal interphalangeal joints with some limitation of motion (Fig. 2). The distal interphalangeal joints were normal. The wrists were slightly swollen and permitted only 5 degrees passive flexion and that with pain. The elbows were not swollen and motion was within 10 degrees of normal. The shoulders were normal in appearance and range of motion. The lower extremities were normal in appearance and function excepting that full passive flexion of the right ankle was painful and there was slight bilateral crepitus of the knees. The spine was normal in every respect.

Laboratory Examinations. Hb. 75%; R. B. C. 4,850,000; W. B. C. 10,400; differential: 66% neutrophils, 14 large lymphocytes, 14 small lymph-

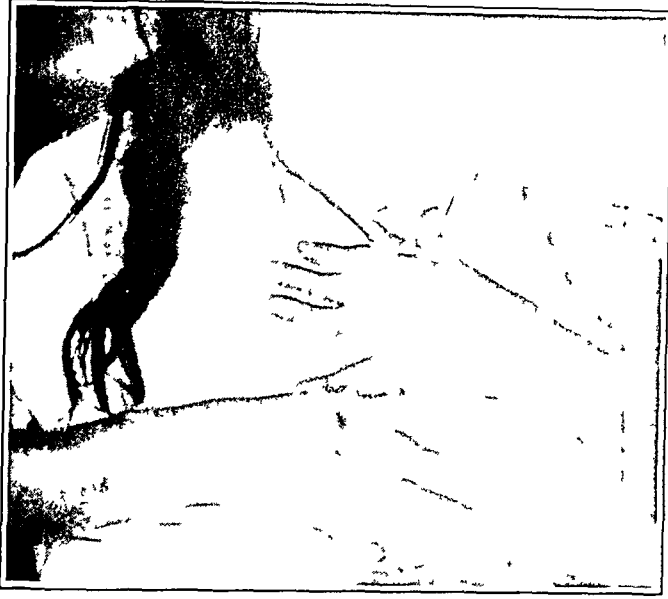


FIG. 1 —Case 1, A. G.

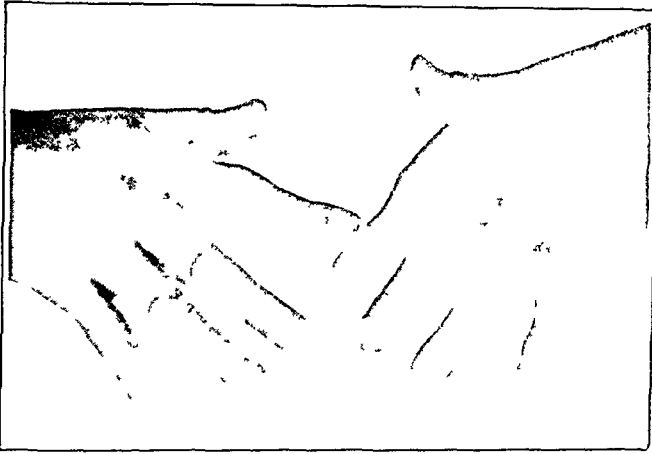


FIG. 2.—Case 1, showing fusiform swelling of proximal interphalangeal joints.



FIG. 4.—Case 2, S. H



FIG. 3.—Case 1, Roentgen ray photograph of left hand and wrist showing demineralization and loss of joint cartilage.



FIG. 6.—Case 2, Roentgen ray photograph of the right hand and wrist showing demineralization and loss of joint cartilage.

ocytes, 6 eosinophils; urine negative; Kahn test negative; sedimentation rate elevated (Cutler method, 23 in 1 hour).

Roentgen ray examination (Fig. 3). Left hand and wrist: There was a low-grade decalcification of all the bones, more marked about the smaller joints. There was definite loss of cartilage of the wrist joints, the middle phalangeal joints and the 5th metacarpophalangeal joints with the latter presenting a lateral abduction due to subluxation. There was no definite fusion between any of the bones. The tips of the terminal phalanges showed a normal degree of bone calcium. The ends of these bones showed some roughening and increased density with a very little overgrowth at the insertions of the capsules. Left elbow: There was little change except for some slight narrowing of the joint space and slight bone atrophy.

This patient was observed in the hospital from January 1, 1936 to February 29, 1936, during which period she had a daily temperature of 99° to 99.2° F. She was given typhoid vaccine intravenously with slight but definite improvement.

CASE 2 (Fig. 4).—S. A. H., a full-blooded female Pima Indian, aged 46, was seen by us in the hospital dispensary. She had been well until about 11 years ago when she first noticed the gradual appearance of pain and swelling in various peripheral joints. She is unable to recall which joints were involved first. About 10 years ago she had all her teeth removed but in spite of this the joint symptoms persisted for several years. She has had very little pain in the past few years, and suffers mainly from the impaired function of her upper extremities. She is of a very low-grade intelligence and is unable to recall much of her past history. She is a widow with 4 living children. She had 1 still-born child. Her menses ceased at about 40 years of age.

Physical examination revealed a fairly well nourished Indian woman, 5 feet tall and weighing 134 pounds. She appeared considerably older than the age recorded in the government census. She presented the following findings: The gums were edentulous and healthy in appearance. The tonsils were atrophic and partially epithelialized. The lungs were clear. The left border of cardiac dullness was at the nipple line. No murmurs were heard. The abdomen appeared normal in all respects. Pelvic examination was refused. The reflexes were normal.

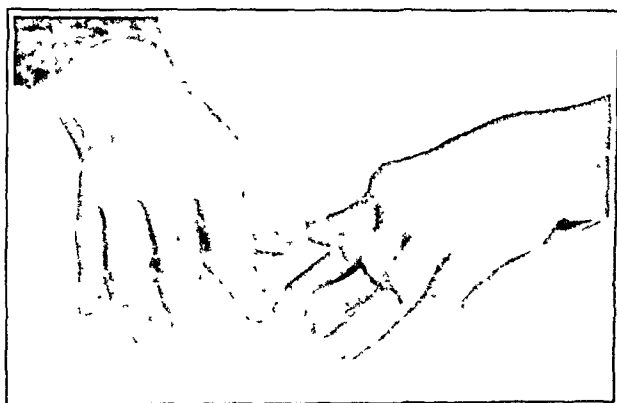


FIG. 5.—Case 2, showing deformity of fingers.

There was marked deformity of the fingers of both hands (Fig. 5) with slight fusiform swelling of the proximal interphalangeal joints and subluxation of the metacarpophalangeal joints, with marked limitation of motion of the latter. No Heberden's nodes were present. The wrists had a fair degree of motion and were not swollen. There was a definite ulnar devia-

tion. The right elbow had only 10 degrees of motion and the left 45 degrees. The elbow joints were not swollen or tender. There was some bilateral limitation of motion of the shoulder joints to full abduction. Except for some crepitation of the knees, the lower extremities were normal in appearance and function. The spine was normal in all respects.

Laboratory Examinations. Hg. 90%; R. B. C. 4,800,000; W. B. C. 11,000; differential: 60% neutrophils, 20 large lymphocytes, 12 small lymphocytes, 6 monocytes, 2 eosinophils; urine negative: Kahn test negative; sedimentation rate elevated (Cutler method, 27 in 1 hour).

Roentgen ray findings (Fig. 6). Both hands, and wrists: There was a moderate decalcification of all the bones. There was fusion of the carpal bones on the left side and bilaterally some loss of cartilage in nearly all of the joints with evidence of subluxation of the metacarpophalangeal joints. In addition to the bilateral destruction of the joint cartilage there were bilaterally a few small areas of erosion of the bone at the distal radial articular surfaces. At the outer margins of the styloid processes of both radius and ulna bilaterally there were some periosteal outgrowths. There were also fine spurs at the radial-volar margins of the heads of the second, third, fourth and fifth right metacarpal bones. Both elbows: There was evidence of loss of cartilage at both elbow joints, more marked on the left side with narrowing of the joint space and some loss of calcium in the ends of the bones. The margins of the bones were smooth.

She was in the hospital from October 17, 1935 to December 20, 1935, with a bronchopneumonia. She had no flareup of joint symptoms at that time and made an uneventful recovery. When the present examination was made, January 30, 1936, her temperature was 99.4° F.

We have not included detailed reports of the third Indian with atrophic arthritis, nor of the one with spondylitis, because they have not spent all their lives on the Reservation. The third case of atrophic arthritis is one of long standing in a full-blooded male Pima Indian, J. N., aged 57. As a young man he worked in New York City for several years but had to return to the Reservation because of the development of epileptic seizures. Some years later he developed pain and swelling of his ankles, wrists, elbows and shoulders. At present he has very little pain in these joints, but there is some slight swelling and definite limitation of motion in all of them. His fingers have never been involved. The past year or two he has had some pain in his spine, probably due to hypertrophic changes, consistent with his present age. He has had to be hospitalized frequently because of his epileptic seizures.

The Indian with spondylitis is a 40-year-old full-blooded Pima who was well until 12 years ago. In his early twenties he spent 5 years at an Indian school in California. Three years after his return to the Reservation, while working as a carwasher in Phoenix he developed pain and swelling of his left ankle. This persisted but he was not incapacitated until 2 years later when he began to have pain and swelling in his knees as well. Shortly after this his right shoulder became involved. After a period of rest his symptoms subsided. He maintained good health for the next 3 years at the end of which time he was given employment in the boiler house on the Reservation. Soon after he returned to work he began to have pain in his left hip followed by a recurrence of pain and swelling in his knees and right shoulder. Gradually the other hip and his entire spine became involved, with progressive ankylosis of the latter. He has been completely bedridden for the past 5 years. On examination it was found that he had manifestly diseased tonsils and teeth and had a slight daily elevation of temperature to 99° F. He was also found to be diabetic, having 3+ sugar in his urine and a fasting blood sugar of 290 mg./100 cc. He is to be brought to the hospital at an early date for the regulation of his diabetes and the removal of the obvious foci of infection present in his mouth.

Neither of these Indians gave a personal nor family history suggestive of past or present venereal infection or showed any physical signs of syphilis or gonorrhea.

These case reports show conclusively that arthritis in its most crippling form does occur among native Indians of the Southwest. To the best of our knowledge there are no statistics on the prevalence of atrophic arthritis, as distinct from rheumatic conditions in general, among an unselected population. Consequently we are not prepared to say whether, in a population of approximately 2700 adults, at least 2 cases of atrophic arthritis occurring among Indians who have lived all their lives on the Reservation represents a high or a low prevalence as compared with what might be found in other climates. Glover,⁴ however, in a study of rheumatic conditions among a large group of British insured, estimates that in an insured adult population (16 to 65 years of age) there will be found 1 case of "rheumatoid" arthritis among 1000 males and among the same number of females 3 cases of "rheumatoid" arthritis. It is of interest to note that there were no persons found suffering from the senile hypertrophic form of arthritis (osteoarthritis) with symptoms severe enough to have been brought to our attention.

Conclusion. In this survey of chronic non-tuberculous joint diseases among approximately 2700 adult Pima Indians 2 cases of severe atrophic arthritis were observed in Indians who had spent their entire lives on the Reservation. As far as these observations go there is no basis for the opinion that the Indians of the Southwest are exempt from this disease. A third case of atrophic arthritis and another of spondylitis with involvement of peripheral joints, both occurring in full-blooded Pima Indians have also been discussed briefly.

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A NOTE ON THE INTESTINAL BACTERIA IN CHRONIC ARTHRITIS.*

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ATTENTION has frequently been directed to the relationship of the gastro-intestinal tract to the problem of chronic arthritis.¹⁴

* The expenses of this investigation were defrayed in part by a grant in memory of Alexander B. Cox.

This relationship is exemplified by frequent disturbances of position, configuration and function of the gastro-intestinal tract and by frequent improvement in these disturbances following institution of measures which permit the establishment of optimal nutrition and other measures which favorably influence both the gastro-intestinal and the arthritic symptoms,⁵ such as control of infection, adequate rest, etc.

Recognition of the significant rôle of infection in precipitating arthritis of various types has been accompanied by few, if any, precise data bearing upon the influence of infection within the gastro-intestinal tract, except in a more or less surgical sense of the word.

There is ample evidence to indicate, however, that the gastro-intestinal tract is in close communication, through the lymph channels or the blood stream, with the joint tissues,^{3,9} and that crystalloids or even particulate matter may thus reach the joint tissues. Arnold and his coworkers^{15,16} have shown that animals given yeast or bacteria by mouth and by rectum may show significant absorption of these into the general circulation and even into various organs, whence the organisms can be recovered. This absorption is expedited apparently by the coincident ingestion of egg albumen. The highest incidence of bacteria in organs or lymph nodes is observed between 15 and 45 minutes after introduction. This work has been corroborated in general by Boone, Chase and Brink,² by Cirrincione and Francona⁴ and by Peirce, Wright, Goldhaft, Stabler and Pemberton.¹³ More recently studies by Muether and Kinsella¹² have shown that if streptococci be ingested by dogs in which experimental lesions of the valves of the heart have been produced, endocarditis and some features suggestive of acute rheumatic fever may arise.

It is clear therefore that some importance attaches to the kind, proportion and numbers of bacteria which inhabit the gastro-intestinal tract of human beings or are introduced into it. Importance also attaches in this connection to the condition of the gastro-intestinal tract as a whole and to the extent to which the passage across the wall of the gut of material of various kinds, including bacteria, is expedited or retarded.

For some time suspicion has existed that the benefits to be observed among some arthritics, following alterations of the food intake, may be referable in part to changes in the substrate thus induced and hence to some phases of bacterial activity within the gastro-intestinal tract. With the aim of approaching this question, preliminary studies were accordingly conducted on the nature of the bacterial flora of the intestine as reflected in the feces of normal subjects as compared with that of arthritic subjects. The influence of certain changes in the substrate, incidental to altered diets, upon the character of the fecal flora was also estimated.

Materials and Methods. In this preliminary study, stools of 9 normal and 17 arthritic persons of both types were examined immediately after passage, macroscopically, microscopically and culturally. The arthritic cases selected for study were those in which a variety of factors was operative though an effort was made to include some in which the gastro-intestinal tract was suspected of playing a significant rôle. The technique employed is subject to some variability but is such as to permit a qualitative and semiquantitative analysis of the various groups of aerobic and anaerobic bacteria.

The influence of certain qualitative differences of diet on the bacterial flora of the intestine is well known. In an attempt to evaluate this factor in terms of the influence of the regular house diet and a "balanced" diet of about 1800 calories, high in vitamin and protein content and relatively low in concentrated carbohydrate foodstuff, studies were made of the stools of both arthritic and normal persons after the ingestion of such rations. In some cases, to be discussed later, the same individual was studied on both diets; also, 3 arthritic patients on the "balanced" diet were studied on admission to the hospital and later after some improvement of symptoms.

Observations by Dr. B. Hampil indicate⁷ that the examination of one stool per case affords a fairly good estimate of what bacteria are present. At intervals of 1 week 5 stools were examined by her from each of 2 cases of osteoarthritis and found to be fairly constant. "While the actual numbers of bacteria were not the same, the relationships between the groups remained the same." In the present studies, examinations were made of more than one stool in many cases.

The defecated specimen was collected in a sterile jar and was brought (with a few exceptions where normal stools were brought in from outside) immediately to the laboratory where the examination was begun at once. One gram of the stool specimen was macerated in a sterile mortar, diluted 1 to 50 with sterile physiologic salt solution, and shaken in a sterile flask with glass beads until thoroughly mixed. Successive dilutions were made from this 1 to 50 dilution in sterile saline, using a sterile 1-cc. pipette for making each dilution. These dilutions, after being thoroughly mixed and shaken, were sown into media selected to demonstrate the presence of the different large groups of bacteria: lactose broth for coliform organisms and streptococci, dextrose-tomato broth for lactobacilli, salt agar for Gram + cocci, sealed cooked-meat tubes for anaerobic organisms. All were incubated in air at 37° C., except one set of tomato agar and broth cultures which were incubated in 10% (approximately) CO₂ at 37° C. to enhance the growth of lactobacilli.

Subcultures were made as follows to determine the various types of bacteria present:

Lactose broth cultures showing acid and gas, or acid alone, were diluted—two loops of culture to 9 cc. sterile saline solution. One or two loops of this dilution were sown on an Endo plate, spread with a glass rod, and incubated at 37° C. for 24 to 48 hours. Isolated colonies were stained and transferred to agar for study. The bacilli were studied in the following respects: motility in tryptophane broth after 2 to 3 hours' incubation; indol production in tryptophane broth after 24 hours; occasionally also, Voges-Proskauer test, Clark-Lubs (methyl red) test, liquefaction of gelatin, gas ratio (fermentation of dextrose in Smith tube), fermentation of other sugars (sucrose, mannite, salicin, and so on).

After the lactose tubes had been incubated for 72 hours, the bacilli were found to have been replaced by streptococci. These were isolated and were examined in respect to morphology in hanging drop (plain broth after 24 hours), Gram stain, and sometimes in respect to the type of hemolysis on blood agar.

Dextrose tomato broth cultures (pH 5.0 or less) were examined every 24 hours for at least a week to determine the presence of lactobacilli. Stained smears were made from those tubes which showed growth. If Gram + rods appeared, subcultures were made on tomato agar plates. Isolated colonies were subcultured in litmus milk, dextrose and gelatin.

Tomato agar poured plates, seeded with the original fecal dilutions, were incubated in CO₂ (Kulp¹⁰ and Kulp and White¹¹) and colonies therefrom were stained after 24 and 48 hours. It was found that considerable quantities of yeasts and molds grew on these plates in CO₂ and obscured the growth of any other organisms, so these plates were later omitted.

Salt agar poured plates were counted after 48 to 76 hours. Colonies were transplanted to plain agar and stained after 24 hours until the types of colonies became familiar. *B. coli* grows on 6% salt agar but not on 8% or 10% (Hill and White⁸). Growth of Gram + cocci was best on 8% salt agar.

Cooked meat tubes, boiled to expel O₂ and sealed with vaseline-paraffin, were observed for growth, gas-production, and proteolysis and were stained at 24, 48 and 72 hours for spore-bearing bacilli. After 2 weeks, some of the broth was drawn off with a sterile capillary pipette and transferred to a sterile tube, heated to 80° C. for 12 minutes in a water bath, and transferred to a fresh meat tube, sealed, incubated, and examined as before. It is justifiable to believe that the heating kills off all non-sporulating organisms and that the growth in the second tube is of *Clostridia* alone.

Macroscopically, the stool specimen was observed in respect to color, odor, consistency and pH.

Microscopically, a saline suspension of a bit of feces was studied untreated for muscle fibers, fat, vegetable cells and protozoa, and with iodine for undigested starch. Smears of the 1 to 50 dilution of 1 gm. of the stool were then studied by the Gram stain, and by the Klieve-Harris stain for spirochetes. A routine fecal examination of each stool was also made in the hospital laboratory.

Experimental Observations. Macroscopically, the arthritic stools studied seemed slightly different from normal stools. The color and consistency of the arthritic stools were decidedly more varied. Some arthritic stools were made up of portions of several different colors and consistencies, whereas the normal stools were usually well-formed and homogeneous. The odor, while not a characteristic easily recorded for purposes of comparison, seemed to be stronger and more foul in the arthritic group. The pH varied between 6.6 and 8.4, being usually 7.4 to 7.6 in the arthritic stools and slightly nearer the neutral point in the normal stools.

Microscopically, arthritic and normal stools presented about the same appearance, except in a few instances where an arthritic stool showed evidences of poor digestion (many muscle fibers and vegetable cells). Protozoa were seen oftener in the normal stools than in the arthritic stools but in no case were they of a pathogenic variety. The activity of the entire flora was about the same in both kinds of stools. The Gram-stain was quite unsatisfactory as a means of differentiation because of the great numbers of dead bacteria present which obscured any estimate of the numbers of viable Gram + and Gram - bacteria present.

Culturally, the total number of bacteria per gram of feces was greater in the arthritic than in the normal individual (Table 1). This difference was obtained generally throughout all the groups of bacteria studied, as may be seen from Table 2, which gives the number of bacteria found in each group studied. These numbers are approximate totals obtained by the dilution method of counting, and represent merely end-points of growth.

TABLE 1.—TOTAL NUMBER BACTERIA PER GRAM OF FECES.

Arthritic.			Normal.	
A series, No.	Type.*	Total bacteria in thousands.	N series, No.	Total bacteria in thousands.
1	H + A	2,075,500	1	517,250
2	A	†	2	60,750
3	A	14,500	3	195,500
4	A	555,050	4	540,000
5	A	1,043,500	5	‡
6	A	50,750	6	6,200
7	A	55,050	7	550,500
8	H + A	10,055,000	8	5,005,500
9	A	705,000	9	500,600
10	A	10,700	10	555,090
11	A	55,100		
12	H	1,001,000		
13	A	10,035,000		
14	A	512,500		
15	A	560,750		
16	H	555,500		
17	A	505,600		
18	H + A	60,500,000		
		Average 5,193,500	Average	881,270

* H = hypertrophic; A = atrophic.

† A 2 cultures unsatisfactory due to high temperature in incubator.

‡ N 5 sample unsatisfactory.

The most notable difference between the arthritic and normal stools is quantitative rather than qualitative. With a few exceptions, all groups of bacteria studied were found to be represented by viable bacteria in every stool, but these bacteria were present in greater numbers in the arthritic stools. As might be expected, coliform organisms occurred in every stool studied. Their numbers were usually not so great as those of the streptococci and not so small as those of the anaërobic bacilli (Table 2). The streptococci were represented by the largest count obtained for any group, and the anaërobic bacilli by the smallest.

A word should be said about the lactobacillus group of organisms. This group is included in the tabulations (Table 2) merely to show that it was given consideration and to record that difficulties prevented separating out these organisms by the simple methods here used. The medium chosen was not selective enough to permit the growth of lactic acid organisms alone, particularly when yeasts or molds were present. When lactobacilli were found to be present, their numbers were included in the totals.

TABLE 2.—KIND AND NUMBER OF BACTERIA IN THOUSANDS PER GRAM OF FECES.

Arthritics.	Coliforms.	Lactobac.	Gr. + cocci.	Streptococci.		Anaerobic bacilli.
				Aërobic.	Microaëro.	
A 1	500,000	500,000	575,000	..	500,000	500
A 3	5,000	500	8,500	0	500	0?
A 4	500,000	0?	5,000	50,000	50,000	50
A 5	500,000	0?	43,000	0	500,000	500
A 6	50	0?	200	50	50,000	500
A 7	50,000	0?	50	0	5,000	0
A 8	5,000,000	0?	50,000	50,000	5,000,000	5,000
A 9	5,000	5,000	195,000	500,000	50,000	5
A 10	5,000	0?	700	500	5,000	5
A 11	5,000	5	0	50	50,000	50
A 12	500,000	0	500	500	500,000+	500
A 13	5,000,000	0	30,000	50,000	5,000,000+	5,000
A 14	5,000	0	2,500	50	500,000	5,000
A 15	50,000	0	10,700	500,000	500,000	50
A 16	50,000	50	410	500	500,000	5,000
A 17	5,000	5	75	0	500,000	500
A 18	5,000,000	50,000,000	18	5,000,000	5,000,000	500,000
Average	1,010,591		54,215	384,480	1,100,600	30,744
Normals						
N 1	5,000	5,000	2,250	5,000	500,000	5,000
N 2	500	5,000	5,200	50	50,000	50
N 3	5,000	50,000	90,000	..	50,000	500
N 4	5,000	0?	35,000	50,000	500,000	50
N 6	50	5	1,100	50	5,000	50
N 7	50,000	0	0	50	500,000	500
N 8	5,000	0	5	50	5,000,000	500
N 9	500	5	5	500	500,000	50
N 10	5,000	500,000	85	50,000	50,000	5
Average	8,450		14,849	13,212	795,000	745

The streptococci were cultivated both aërobically and micro-aërobically. No attempt has been made to separate these groups since most streptococci are facultative and are viable under both sets of conditions. In order to avoid the possibility of counting them twice, the larger of the two groups was regarded as representing the number of streptococci present. In several cases (A 3, A 5, A 7, A 17) streptococci failed to grow aërobically but were viable under micro-aërophilic conditions. This observation may be significant since these cases were all arthritic and the phenomenon did not occur in the normal series. In no case, either arthritic or normal, did streptococci fail to grow under conditions of reduced oxygen tension.

Gram + cocci (exclusive of streptococci) were found in variable numbers in all stools except two, 1 arthritic and 1 normal.

The anaerobic cultures of stool suspensions were carried only far enough to ascertain the presence of Gram + rods bearing heat resistant spores (80° C. for 12 minutes) which would germinate in an anaerobic medium. This group was represented in all stools except two arthritic ones.

The results of bacterial study obtained in cases where the diet was controlled, may be divided into two parts. In Series I (Table 3)²

arthritic and normal persons were studied first on the "house" diet (usually rather high in carbohydrates) and later on the "balanced" diet. This series was undertaken as a control, to find out whether the diet influenced the stool flora in those cases. Of the 2 normal persons examined, 1 was active and 1 was in bed; all 3 arthritics were confined to bed. The results of this short series did not lead to any decisive conclusion.

The purpose of Series II (Table 3), was to determine whether amelioration of symptoms was accompanied by any change in the numbers of intestinal bacteria. A reduction in numbers or a change in the direction of the average normal count might be regarded as having significance. Three arthritic patients were studied upon admission to the hospital and later after some clinical improvement in the patient had occurred. The "balanced" diet was employed for at least 4 days prior to examination and throughout the rest of

TABLE 3.—COMPARISON OF FECAL FLORA IN DIET-CONTROLLED CASES. BACTERIA GIVEN IN THOUSANDS PER GRAM.

Series I.

Normal and Arthritic Patients on House Diet and on "Balanced" Diet.

Diet.	Coliforms.	Lactobac.	Gr. + cocci.	Streptococci.		Anaerobic bacilli.	Total.
				Acrobie.	Microaero.		
House	500	5	5	500	500,000	50	500,560
N 9	5,000	500,000	85	50,000	50,000	5	555,090
N 10							
Balanced	5,000	50	10	500,000	500,000	50	505,110
N 9	500	5,000	450	500	5,000	5	10,955
N 10							
House							
A 1	500,000	500,000	575,000	.	500,000	500	2,075,500
A 10	5,000	0	700	500	5,000	5	10,705
A 11	5,000	5	0	50	50,000	50	55,055
Balanced							
A 1	50,000	5,000	94,000	..	500,000	0	649,000
A 10	5,000	0	0	500	500,000	50	505,050
A 11	500,000	0	0	500	5,000,000	50,000	5,550,000

Series II.

Arthritic Patients Before and After Clinical Change.

	Coliforms.	Lactobac.	Gr. + cocci.	Streptococci.		Anaerobic bacilli.	Total.
				Acrobie.	Microaero		
On admission							
A 16	50,000	50	410	500	500,000	5,000	555,460
A 17	5,000	5	75	0	500,000	500	505,580
A 18	5,000,000	50,000,000	18	5,000,000	5,000,000	500,000	60,500,018
After treatment							
A 16	50,000	5	35	5,000	500,000	5,000	550,040
A 17	500	5	30	0	500,000	500	501,035
A 18	5,000,000	500,000	1,920	5,000	5,000,000	50,000	10,551,920

the experiment. Diagnostic studies of the alimentary tract usually intervened between the two examinations, though at a period so far removed as not to interfere with the second bacteriologic examination. All cathartics were withheld for at least 4 days previous to a bacteriologic study.

It would have been desirable to omit all attempts at lubrication. In practice, however, it was impossible to achieve this because of

the fact that, in some arthritics, no stool would have been forthcoming without assistance of some kind. The recognized tendency of many cases in this group toward intestinal stasis made the routine use of mineral oil necessary.

It might be argued that artificial expedition of the intestinal contents permits the recovery from the stool of some viable bacteria which might otherwise die in the lower colon. This conjecture cannot be put aside entirely but does not seem adequate alone to explain the findings here recorded. Under the above regulation, the arthritics as a group experienced no more frequent or larger evacuations than did the normals.

The total numbers of bacteria were of about the same magnitude on admission and after treatment. There were some slight changes in each individual but none which occurred consistently throughout the series. The relationships between the groups of bacteria in each stool remained the same after treatment, the group which was largest on admission remaining the largest group after treatment, and so on. It is interesting to note that 4 of the arthritic cases (Table 2) showed no viable aerobic streptococci. In the case of A 17, there were no aerobic streptococci either before or after 2 weeks of treatment during which period great improvement was shown.

Summary and Comments. The bacteriologic studies here described constitute an approach to the problem of the nature and possible influence of the intestinal flora in atrophic and hypertrophic arthritis. The series is a short one but serves to indicate the general respects in which normal and arthritic stools may differ. The observation that greater numbers of bacteria occurred in the stools of the arthritic persons studied than in those of normal persons may be significant.

The numerical relationships between the different groups of bacteria are difficult of delineation but are approximately the same in normal and arthritic stools. The only difference observed was chiefly one of magnitude, as in the case of the total counts.

These studies suggest that there are greater numbers of bacteria in the intestine of some arthritics, of each type, than are encountered with supposedly normal persons. Some explanation of this is perhaps to be found in the frequency with which arthritics present anatomic and functional departures from normal in the gastrointestinal tract, especially the large bowel.^{5,14}

The groups of bacteria studied were encountered with the following incidence: (a) *Coliform organisms* in every stool studied; (b) *Gram + cocci* (exclusive of streptococci) in all stools except 1 arthritic and 1 normal; (c) *Anaerobic bacilli* in all except 2 arthritics; (d) *Streptococci (micro-aerophilic)* in all stools; *Streptococci (aerobic)* in all normal stools and in all but 4 arthritic stools. The omnipresence of some strain of streptococcus in normal as well

as arthritic stools indicates the possible impropriety, on the basis alone of recovery of it from the feces of arthritics, of attaching specific significance to this organism.

The dietetic studies recorded are preliminary and suggest that the diet used does not alone determine the numbers of intestinal bacteria. It appears that other influences are also active in maintaining the intestinal flora. Treatment along various lines, including dietetic, with coincident improvement of symptoms, was not accompanied by any observable change in the nature of the established intestinal flora.

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TYROSINEMIA AND ITS RELATION TO PATHOLOGY OF THE LIVER.*

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THE appearance of tyrosin and leucin crystals in the urine of patients with acute yellow atrophy of the liver was first described by Frerichs.³ For many years these crystals have been considered pathognomonic of the disease. In recent years much doubt has been expressed about the significance of this finding. Umber⁷ estimated that tyrosin and leucin are demonstrable in approxi-

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mately one-third of the cases, while Bergstrand¹ stated that tyrosin crystals are found in only a small percentage of the cases. Hence it would appear that the absence of tyrosin crystals from the urine does not rule out the diagnosis of acute yellow atrophy. Furthermore, tyrosin crystals have been found in the urine of patients with other liver conditions associated with jaundice (Eppinger and Walzel²).

A method more specific and sensitive than the crystallographic for the detection of tyrosin in the urine is the tyrosinase method described by Lichtman and Sobotka.^{6a} Lichtman^{6b} has been able to demonstrate tyrosin in the urine of approximately 30% of cases with disease of the gall bladder, bile passages and liver. The tyrosinuria occurred most frequently in patients with acute and subacute degeneration of the liver, and less frequently in patients with malignant disease of the liver and bile passages, obstructive jaundice due to stone and toxic (arsphenamine and cinchophen) or catarrhal jaundice. He also reports the appearance of tyrosin in the urine in cases of degenerating carcinoma of the lung and in dermatitis exfoliativa. Since we feel that the source of the tyrosin in these cases is tissue breakdown, the tyrosin must first pass into the general circulation before appearing in the urine. In view of this fact and also in view of the possibility of a threshold value for blood tyrosin, we have attempted a study of the occurrence of tyrosin in the blood of normal individuals and of patients with and without liver disease.

Methods. The presence of free tyrosin in the blood was determined by a modification of the method of Folin and Marézi⁴ for the analysis of tyrosin in proteins. The steps in the procedure were as follows: 20 cc. of a Folin-Wu blood filtrate were placed in a 50-cc. centrifuge tube and 4 cc. of a solution of 15% HgSO_4 in 6N H_2SO_4 added; the mixture was allowed to stand 2 hours, the resulting precipitate containing tryptophane and cystine derivatives; the supernatant fluid obtained after centrifugation of the mixture was decanted into a 50-cc. volumetric flask; 12 cc. of a solution of 1.5% HgSO_4 in 2N H_2SO_4 were added to the residue in the centrifuge tube, the residue broken up, and the mixture centrifugated again; the supernatant fluid was added to the volumetric flask; the residue was washed once more, this time with 5 cc. of 0.1N H_2SO_4 , centrifugation repeated and the supernatant liquid decanted into the volumetric flask; the flask was shaken to insure mixing of the contents, and placed in a bath of boiling water for 5 minutes, at the end of which time it was removed and cooled in running water; when thoroughly cooled 1 cc. of 2% NaNO_2 was added, the mixture carefully shaken and allowed to stand for 2 minutes, at the end of which time the readings were made. In order to facilitate the detection of the pink coloration, indicating a positive test, the flasks were observed against a white background, using a similar flask containing distilled water as a control. The amount of free tyrosin detected in each of the positive tests was insufficient to be quantitated colorimetrically, hence designations of strongly positive (+++), positive (++), faint (+) or negative were utilized, according to the intensity of the pink coloration present in the final solution after the addition of the sodium nitrite.

Since phenols other than tyrosin give a positive test with the above method of analysis, it was necessary to determine whether the positive tests obtained in the cases here reported were due to tyrosin. This phase of the problem was studied by checking the results obtained by the method cited above with an enzymatic method for the detection of tyrosin. This was done by the technique as outlined by Lichtman and Sobotka^{6a} for the detection and estimation of tyrosin in the urine. In the present work, 4-cc. samples of blood filtrate prepared by the Folin-Wu method were placed in test tubes 150 by 20 mm., fitted with side-arms. One cc. of a 0.2 M phosphate buffer solution (pH = 6.8) was added, making a total volume of 5 cc. The phosphate buffer was made up of equal parts of solutions of KH_2PO_4 (27.23 gm. per 1000 cc.) and $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$ (35.62 gm. /1000 cc.). From 50 to 100 mg. of tyrosinase, freshly prepared from minced potato, were added. The samples were aerated for 120 minutes by a current of air drawn through capillary tubes to insure constant agitation and equal distribution of the enzyme. The pressure was equalized through a central wash bottle, the stopper of which was perforated to admit connections to the side-arms of the test tubes, also a vent and an outlet. One drop of caprylic alcohol was added to prevent foaming. Two control tests, one with boiled tyrosinase and the other with known tyrosin solution to determine the potency of the tyrosinase were also conducted. The procedure was carried out at room temperature and observations made at 1, 3, 7 and 24 hours. The final colors obtained at the completion of the reactions varied from slate to violet. The reaction here consists essentially of the conversion of tyrosin into a rose-colored substance by the action of the enzyme tyrosinase, with the non-enzymatic formation within 24 hours of melanin, this latter phase of the reaction adding to the specificity of the test. It has been noted by others that the first phase of the reaction may be obtained with such substances as tryptophane, cresol, adrenalin, polypeptid chains containing tyrosin, aromatic hydroxy amines and hydroxy acids and sodium salicylate. However, the second phase of the reaction, namely, the formation of of melanin, is not obtained with any of the above-mentioned substances.

Observations. Our observations as to the presence or absence of free tyrosin in the blood were made first on 14 healthy young adults under fasting conditions. The total phenol and tyrosinase

TABLE 1.—CONTROL CASES. PATIENTS WITHOUT DEMONSTRABLE LIVER DISEASE. TYROSIN ABSENT IN THE FASTING BLOOD.

Diagnosis.	No. of cases.	Diagnosis.	No. of cases.
Cardiac	42	Acute infections:	
Hypertension	5	Influenza	4
Kidney	13	Tonsillitis	6
Pneumonia:		Otitis media	2
Lobar	28	Rheumatic fever	3
Broncho	12	Adenitis	2
Bronchiectasis	8	Diabetes mellitus	24
Asthma	5	Hyperthyroidism	2
Pleurisy	4	Trichiniasis	3
Pulmonary tuberculosis	15	Helminthiasis	1
Peptic ulcer	13	Alcoholism, acute	6
Cholecystitis	10	Iodine ingestion	2
Gastritis	4	Arthritis	6
Gastro-enteritis	2	Arsphenamine-treated lues	20
Constipation	2	Tabes dorsalis	3
Cerebral accidents	11	Miscellaneous	10
Epilepsy	3		
Skin diseases	3	Total	274

tests were performed at the same time in every case. In none of these cases was tyrosin found by either test. Observations on 274 patients without demonstrable liver lesions were then made. In this group, there were cases presenting disease of practically every system of the body as outlined in Table 1. None of these cases showed any trace of tyrosin in the blood when it was obtained in the morning under fasting conditions. One hundred and forty-seven non-fasting controls were also studied. In this group of cases a great variety of pathologic changes were also present. These cases were selected only from the point of view that there was no demonstrable change within the liver. One hundred and thirty-three cases showed no trace of tyrosin by either test, but in 14 cases a trace of tyrosin was found. Of these 14 cases, 10 were reëxamined under fasting conditions and in none of them was any tyrosin demonstrated in the blood. Finally, 51 cases with demonstrable biliary tract disease (gall bladder disease was not included), with and without jaundice, were studied under fasting conditions. In this group, 41 cases showed a variable amount of tyrosin in the blood by both the chemical and tyrosinase methods and 10 showed none. By our method of blood study, then, we have been able to demonstrate the presence of tyrosin in approximately 80% of the cases showing liver disorder, as compared with the 30% shown by Lichtman as a result of urinary studies.

Table 2 shows the diagnoses made and the number of cases

TABLE 2.—CASES WITH LIVER INVOLVEMENT SHOWING THE AMOUNT OF TYROSIN PRESENT WITHIN THE FASTING BLOOD IN THE VARIOUS CONDITIONS INVESTIGATED.

Diagnosis.	No. of cases.	Degree of tyrosinemia.			
		None.	Traces.	Positive.	Strongly positive.
Cirrhosis of liver	25	2	13	9	1
Acute hepatitis	6	1	3	2	
Arsphenamine-treated lues	3	..	3		
Arsphenamine jaundice	1	..	1		
Weil's disease	1	1
Subacute yellow atrophy	2	1	1
Cholecystitis and cholangitis . . .	1	..	1		
Cancer of pancreas	5	3	1	1	
Cancer metastasis	4	2	2		
Leukemia with liver involvement . .	1	1	
Pigment cirrhosis	1	1	
Luetic cirrhosis of liver	1	1			
Total	51				

studied. It also shows the amount of tyrosin found in the various cases studied. The positive tests in this series were shown by the tyrosinase method to be due to tyrosin.

Comment. Clinically, tyrosin appears in the urine only in cases of liver disorder (Lepehne⁵), with the possible exception of rapidly degenerating tumors and extensive lesions of the skin.^{6b} As demon-

strated in our studies, free tyrosin in traces may appear in the blood following a protein meal. Under fasting conditions tyrosin cannot be demonstrated in the venous blood in normal persons. We have demonstrated tyrosinemia in patients with liver disease. Therefore we feel justified to state that in the absence of rapidly degenerating tumors and extensive skin lesions, any free tyrosin demonstrated in the venous blood of fasting patients can be referred to liver disease. The reverse does not hold true. Liver disease may exist without tyrosinemia. The amount of tyrosin in the blood is seemingly directly dependent upon the amount of liver cell involvement and does not necessarily parallel the degree of jaundice. One case of acute yellow atrophy, however, showed no tyrosin at all. On the other hand, we have repeatedly observed diminution of the blood tyrosin in a patient with Weil's disease and in patients with catarrhal jaundice as they improved.

Of special interest are the cases of obstructive jaundice, which included 5 cases of cancer of the head of the pancreas and 3 cases of cholecystitis and cholelithiasis with jaundice due to cholangitis, stone or stones in the common bile duct. Two of the 5 pancreatic carcinomas showed some free tyrosin in the blood, while 3 showed none. One case without tyrosin showed at autopsy no liver involvement, while 1 with tyrosin in the blood showed considerable liver destruction. The case of cholangitis showed a trace of tyrosin in the blood, while the cases of stone obstruction of the common duct showed none. Further observations may confirm our impression that tyrosin is absent in the blood of obstructive jaundice patients as long as there is no liver involvement. Twenty-five cases of cirrhosis of the liver were studied. In this group, 23 had from traces to strongly positive tests for tyrosin in the blood, and 2 had none. These cases will be discussed in more detail in a forthcoming contribution. At present we are unable to correlate tyrosinemia with the presence or absence of jaundice.

Since arsphenamine treatment may cause injury to the liver, 23 such cases were studied. In 3 cases, traces of tyrosin were demonstrated within the blood although there was no other evidence of liver damage.

In malignancy with liver metastasis, the tyrosin test does not seem to be of any practical value. Five cases were observed; in 3 cases, tyrosin was demonstrated; in 2 none.

An attempt was made to correlate the tyrosin contents with that of total amino acids in the blood. In none of the cases studied in which tyrosin was found in the blood did we find an increased total amino nitrogen. Other observations were also made in the positive cases as to the utilization of intravenously injected galactose, the Takata-Ara test on the blood serum and the icteric index. These data will be presented in a future paper.

Conclusions. Free tyrosin can be demonstrated in human blood by comparatively simple tests without exposing the patient to any inconvenience besides a venipuncture. The appearance of tyrosin in the fasting blood is indicative of liver disease, but the absence of tyrosin does not exclude it. It is probable that in obstructive jaundice tyrosin does not appear in the venous blood as long as there is no involvement of the liver. In hepatic jaundice, there seems to be a rapid diminution in the blood tyrosin as recovery takes place. We have been able to demonstrate tyrosinemia in 80% of the cases with liver disease.

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REPEATED ADMINISTRATION OF AMYTAL.

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THE wide use of "Amytal" (Iso-Amyl Ethyl Barbituric Acid, Lilly) has prompted inquiries as to whether any harmful effects result from its continuous administration.^{15a} The question of habit formation has been mentioned particularly.^{15b} By inference to barbitol one is apt to assume that there might be a habit formation with "Amytal" if the drug were repeatedly consumed by an individual.^{12,14} The matter is of great importance both academically and practically, for if true, there should be a more restricted control of its prescription, but if not true the suspicion could be definitely dismissed. It was for the clarification of this situation that the present investigation was undertaken.

A typical habit-forming drug like morphine produces by repeated administration: *a*, tolerance; *b*, euphoria; *c*, diminution of toxicity and, *d*, symptoms of withdrawal. Thus, a habituated subject derives a pleasurable sensation and requires a larger quantity of the alkaloid for narcosis than a non-habituated individual. He will not show toxic signs with a dose which usually kills a normal person. If the use of morphine is interrupted, he will experience a state of

marked discomfort which can only be relieved by the resumption of the drug. These effects, except euphoria, can be readily demonstrated in animals, especially dogs and monkeys, as reported by Plant and Pierce,¹⁴ Tatum, Seevers, and Collins,²³ Schmidt and Livingston,¹⁸ and Seevers.¹⁹

In the present work, experiments were carried out in both dogs and monkeys by repeated use of the soluble salt "Sodium Amytal" (Sodium Iso-Amyl Ethyl Barbiturate, Lilly). A group of 10 dogs was employed: 5 of them were given by mouth a dose of 40 mg. per kg., dispensed in capsules, 3 times a week for 2 months, and the remaining 5 were given the same dose, also 3 times a week, but for 4 months. This amount of "Sodium Amytal"—being equivalent to approximately one-third of the oral minimal lethal dose (125 mg. per kg.) and larger than the therapeutic dose in men—was necessary in order to secure and compare definite hypnotic effects and to overcome the natural tendency in animals, particularly under observation, to fight sleep. The daily administration of this relatively large dose would interfere with the animal's food intake and muscular activity, especially because complete recovery from ataxia occurred 10 to 14 hours after each dose, which accounts for alternating the days of medication. It was found that in the 10 dogs repeated administration of this dose, for either 2 or 4 months, uniformly produced sleep each time. No evidence of tolerance was observed since the same dose, repeatedly employed, was always effective and never failed. The duration of hypnosis varied from day to day, and from animal to animal. On the average, it exceeded 4 or 5 hours, as shown in Table 1. In most cases, the animals

TABLE 1.—REPEATED ORAL ADMINISTRATION OF "SODIUM AMYTAL," 40 MG. PER KG., IN DOGS.

Dog No.	Sex.	Body weight.		"Sodium Amytal"		Average duration of sleep per dose, hrs.
		Initial, kg.	End of experiment, kg.	Total No of doses.	Total amount per animal, gm	
1	M	12 4	14 6	25	13 49	4 52
2	M	14.8	16 6	25	15 40	4 88
3	M	14 1	15 6	25	15 10	5 11
4	M	11 4	13 2	25	13 20	4 22
5	M	19 0	21 4	25	21 40	5 77
6	F	10.8	14 7	50	26 60	4 31
7	F	19 4	21 0	50	39 06	4 87
8	F	10 4	11 9	50	22 20	4 10
9	F	19 2	22 9	50	41 00	4 73
10	F	16.0	19.3	50	35 00	5 05

slept longer with the first 2 or 3 doses than with subsequent doses. This is probably due to the acquired ability of the organism to eliminate the barbiturate at a faster rate, after it has become accustomed to the drug, than at the very start, an explanation already advanced by Eddy.⁵ Toward the end of the observation periods, all animals gained in body weight, ranging from 1.5 to

3.9 kg. (Table 1). The total amounts of "Sodium Amytal" ingested by the animals varied according to their body weight. One dog (No. 9) had received at the end of the fourth month 41 gm. of the drug.

Two or 3 days following the last dose, the amytalized dogs were injected intravenously with a minimal lethal dose of "Sodium Amytal," that is, 75 mg. per kg., as previously determined.^{22a} Dogs 3, 4, 5, 6 and 7 died with this dose while the remaining 5 survived. After a rest of 2 weeks, 2 of the surviving animals died with a dose of 80 mg. per kg. Obviously, there is practically no decrease in toxicity by repeated administration.

Two additional dogs, in connection with another study, received 47.3 mg. of "Sodium Amytal" per kg. of body weight 3 times a week. After the sixtieth dose, these animals were sacrificed, and careful postmortem examinations were made. The visceral organs were studied both grossly and microscopically. It was noted that one dog had cloudy swelling and fatty degeneration in the liver, and the other an abscess in the right renal cortex. Since these lesions were not common to both, it is not likely that "Sodium Amytal" was the causal factor here. The abscess formation in the kidney was certainly an accidental event. The results appear, therefore, in agreement with those of Ravdin, Drabkin, and Bothe,¹⁶ who showed that repeated injections of "Sodium Amytal" in rats have no effect on the various viscera.

In a group of 6 monkeys, "Sodium Amytal" was injected intravenously, 3 times a week, for 6 months. An anesthetic dose which varied from 35 to 40 mg. per kg. was adopted (Table 2). The

TABLE 2.—REPEATED INTRAVENOUS INJECTIONS OF A MINIMAL ANESTHETIC DOSE OF "SODIUM AMYTAL" IN MONKEYS, 3 TIMES A WEEK, FOR 6 MONTHS.

Monkey No.	Sex.	Body weight.		"Sodium Amytal."			Average duration of anesthesia per dose, min.	Average duration of sleep per dose, min.
		Initial, kg.	End of experiment, kg.	Amount per dose, mg. per kg.	Total No. of doses.	Total amount per animal, gm.		
1	M	3.70	4.84	40	82	14.03	52	80
2	F	4.96	5.08	40	82	16.68	51	87
3	M	4.22	5.04	40	82	15.86	53	82
4	F	4.18	3.90	35	75	10.90	47	77
5	F	4.90	4.78	35	80	13.06	51	78
6	M	4.30	4.32	35	80	15.73	51	76

same physiologic responses occurred after each injection; that is, anesthesia and hypnosis. The duration of anesthesia was relatively constant at various stages of experimentation, the average being from 47 to 53 minutes (Table 2). As in dogs, the duration of sleep varied somewhat. It was longer during the first week than during subsequent weeks. No complete loss of effect was ever observed. Four monkeys gained in weight while the other 2 lost slightly. The total amounts received by these animals in the 6 months varied

from 10.9 to 16.7 gm. per animal. After the completion of the last injection, all the animals were observed daily for 3 or 4 weeks. None of them appeared to have any withdrawal signs, such as restlessness, yawning, lacrimation, vomiting, diarrhea, and so on. For fear that any tolerance which might be built up would partially disappear owing to the relatively long intervals between injections, as is the case with morphine,¹⁹ 2 monkeys were given daily injections for 4 weeks, including Sundays. At the end of this period, no increase in dosage was necessary in order to elicit the same effects.

The above data, both in dogs and monkeys, seem to indicate definitely that prolonged use of "Sodium Amytal" is not followed by pathologic changes or habit formation. No tolerance is developed, and no withdrawal symptoms or decrease in toxicity can be demonstrated by repeated administration. The picture is in strong contrast with that of morphine as reported by different authorities.^{14,23,18,19}

There is an apparent agreement between laboratory and clinical results. Hoge⁹ reported a case of a woman, aged 41 years, who had taken 3 to 4 "Amytal" tablets (90 mg. each) daily for a period of 7 years. A careful examination revealed a few subjective nervous symptoms, a moderate tachycardia, and a slight anemia. The author concluded that surprisingly little harm seemed to have followed these large overdoses of "Amytal." Similarly, Lundy and Dixon¹³ described a case of an inoperable brain lesion in which doses of 0.2 gm. of "Sodium Amytal" were administered at hourly intervals for approximately 4 months. A total quantity of 600 gm. was finally consumed. Bleckwenn,³ too, mentioned a case in which 250 daily doses of 1 to 1.4 gm. of "Sodium Amytal" were injected intravenously. No pathologic changes were noted, and apparently no habit formation was suspected. Weiss,²⁵ in discussing the whole group of barbiturates, conceded that if the scientific definition were adhered to, no habit formation would result from them.

Although "Sodium Amytal" appears to have no inherent property of habit formation, there is a group of constitutionally psychopathic inferior individuals who are unable to face the circumstance and thus seek a shield or shelter in drugs, particularly depressants and hypnotics, such as the bromide, "Amytal," and so on. These substances tend to dull their sensorium and relieve them from the sense of responsibility. Occasionally these persons increase the quantities of drugs taken at intervals or daily in order to obliterate completely their unpleasant experiences. If the continuous use of such drugs is interrupted, the mental conflict returns and usually manifests itself in somatic complaints unless the medication is resumed. This has been interpreted (contrary to scientific findings) as evidence of addiction or habit formation of certain drugs, such as the bromide or "Amytal" which the patient happens to take repeatedly. As a matter of fact, the individual can be "habituated."

ated" to any substance that may ameliorate his complaints. In these individuals the clinician should promptly recognize the etiology and avoid the use of, or use with great care, a hypnotic drug such as sodium bromide or "Sodium Amytal."

It has been repeatedly stated that barbitol causes habit formation.^{26,1} Deduction is therefore natural that "Sodium Amytal" will likewise induce the same undesirable effect, since both barbitol and "Amytal" are derivatives of barbituric acid. Most contentions for the barbitol habit can be explained on a psychopathic basis,^{17,24} that is, those persons who continuously ingest barbitol usually belong to the constitutional psychopathic inferior type. Furthermore, the work and experience of Bachem,² Eddy,⁵ and Gillespie⁷ seem to have ruled out the possibility of habit formation by barbitol. Assuming for a moment, however, that the constant use of barbitol would lead to habit formation, it does not necessarily follow that "Amytal" will have an entirely parallel action. Evidence is accumulating that slight modification in the chemical structure results in differences of action. For example, an anesthetic dose of "Amytal" inhibits the action of the vagus,¹¹ while an equivalent amount of pentobarbitol does not.^{22b} Barbitol is excreted in urine but "Amytal" is probably destroyed in the body.²⁰ Phenobarbitol appears to be the most efficacious in the control of epileptic attacks.⁸ "Amytal" surpasses barbitol in its anticonvulsant action.¹⁰ Barbitol is a much longer acting drug than "Amytal."⁶ The compound 1:3-dimethyl-butyl-ethyl barbituric acid produces convulsions instead of hypnosis.² No general conclusions, therefore, can be safely made without investigating the individual substances.

Summary. In 10 dogs given orally approximately one-third of the minimal lethal dose 3 times a week for 2 to 4 months, and in 6 monkeys injected intravenously with an anesthetic dose 3 times a week for 6 months, no evidence of tolerance, withdrawal symptoms, or decrease in toxicity was observed. Each dose was followed by the characteristic effects, such as hypnosis. These results are interpreted as proof against the possibility of habit formation by the prolonged use of "Amytal."

At the end of experimentation, the treated animals appeared to be in good health. All the dogs and 4 of the 6 monkeys gained in body weight. Two additional dogs studied for 20 weeks with repeated administration of "Sodium Amytal" showed, after sacrifice, no uniform pathologic lesions which could be attributed to the drug.

We wish to acknowledge our indebtedness to Messrs. William E. Fry, Brown Robbins, and Herbert Glick for their valuable assistance in the numerous observations recorded here.

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THE PERITONEAL CYTOLOGIC RESPONSE: AN EXPERIMENTAL STUDY.

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As early as 1885, Mikulicz¹⁰ attempted to immunize the peritoneum by means of an *Escherichia coli* vaccine. He was, however, forced to give up the practice because of the severe reactions encountered. Issaëff and Ivanoff,⁵ who used non-specific substances, were more successful a decade later. Since that time much study has been devoted to this type of therapy.

Many substances have been administered intraperitoneally to human beings. The two serums of Weinberg,² which are prepared by immunizing horses with anaërobic organisms and the *Escherichia coli*, are still employed. Good results have been reported by Potter and Coller¹⁴ and by Steinberg and Goldblatt^{15a, b} with the latter's "coli-bactragen." Rixford,^{15a} Jacobs⁶ and other investigators have used a bacteriophage. Johnson and his associates^{7, 8} and Young and Marks²² have used a concentrate of bovine amniotic fluid. Dixon and Barga² (1935), in a report of 1500 cases in which patients were subjected to operations which involved the colon, said that there had been a 66% reduction in mortality from postoperative peritonitis since the inauguration of the use of a vaccine which is prepared from *Escherichia coli* and streptococci.² Herrmann,⁴ in 1928, had administered a nearly identical vaccine to dogs and proved its efficiency in preventing peritonitis caused by fecal soiling.

In the study of peritoneal immunization one is concerned with two distinct processes. The first is the true immune process in

* Throughout this paper the term "Barga's vaccine" denotes this antiperitonitis vaccine; not the better known "specific antibody solution" used in the treatment of chronic ulcerative colitis.

which the introduction of a vaccine into the peritoneal cavity produces a generalized immunity in which the peritoneum shares. The second is the local protection to the peritoneum which is attributable to a local hyperleukocytosis and is afforded by the intraperitoneal introduction of any of a number of vaccines or other substances. I am here concerned only with this latter process.

Cytologic studies have been made on experimental animals, following intraperitoneal injection of many non-specific substances, such as peptone broth,³ saline solutions,^{3,17a,12} sterile water,^{17a} horse serum,^{17a} egg albumen,^{17a,20} solutions of dextrose,¹² and so forth. To the injection of such substances the peritoneum responds by the production of a cellular exudate, the characteristics of which are, in all instances, qualitatively nearly identical. In attempting to produce this "local protection" one should be careful to choose a substance which, when injected, will act as a stimulant, not as an irritant. However, it is true that any stimulant, if used in sufficient concentration, will act as an irritant, and, *vice versa*, any irritant, if diluted enough, will have only the properties of a stimulant. An irritant should, of course, be avoided, as it will only create fertile ground for an infection.

It has been my purpose merely to study the cellular response of the rabbit's peritoneum following the injection of two substances. Bargaen's vaccine has been used because of the present interest in its clinical use; sodium ricinoleate has been used because of certain recent hopeful claims made because of its detoxifying and bactericidal property. This study was stimulated by similar work on the rat by Seeley, Higgins and Mann.^{17b}

The rabbit is a particularly suitable animal for peritoneal studies. Like other animals whose peritoneal fluid normally contains a small number of cells, it is susceptible to peritoneal irritation and peritonitis. The peritoneal fluid of the dog¹¹ and the horse,¹¹ as well as that of man,^{15b} likewise contains a small number of cells and peritonitis is, of course, very common among these species. On the contrary, animals such as the rat, whose normal count is 50 times that of the rabbit, are practically immune to peritoneal infections.

Method. The following technique, which is the same as that employed by Montgomery,¹¹ has been used. The abdomen of the healthy adult animal (approximately 2 kg. in weight) is shaved and cleansed with alcohol. A small pipet which has been drawn out to capillary dimensions at one end is pierced through the abdominal wall. The peritoneal fluid runs up readily into the body of the pipet, which is then withdrawn. The fluid is blown out onto a clean glass slide. The cells in the peritoneal fluid are counted by using the ordinary pipet which is employed in counting the leukocytes of the blood. From the same sample, smears are prepared for differential study and are stained with Wright's stain.* Control values

* In a preliminary group of animals which had received injections of Bargaen's vaccine, the cells in the peritoneal fluid could not be counted after the 3-hour interval because of clotting in the diluent. The clotting is theoretically attributable to an excess of serosomucin, which is precipitated by acetic acid.¹⁹ A 1% solution of hydrochloric acid was subsequently found to be an entirely satisfactory diluent.

were set up by making 124 counts on 49 rabbits and by making 100 differential counts on 42 rabbits. The means and probable errors were calculated, and these values were used for comparison with the values obtained after the experimental injections.

For all practical purposes there are but two types of cells in the rabbit's peritoneal cavity, the monocyte and the neutrophil. Extensive studies of peritoneal cells have been made by Maximow,⁹ Pappenheim,¹³ and Cunningham.¹ Much space has been devoted to the predominant cell, a large active phagocyte which has been variously called "monocyte," "histocyte," "macrophage," "clasmatocyte," and so forth. Whatever its name, it now seems to be established that this cell arises from centers along the blood vessels of the omentum and to a large extent from the subperitoneal tissues in general. No attempt has been made to differentiate lymphocytes in this study, and if such really exist in the rabbit's peritoneum they have been classed with the monocytes.

Although neutrophils are almost accidental findings in the normal unstimulated peritoneal cavity (forming on the average about 0.5% of the total count), they are found in large quantities following intraperitoneal injections. In the rabbit these cells are nearly all of the pseudoeosinophilic type, which have been described adequately by Scarborough¹⁶ and others. In all probability they come into the peritoneal space from the blood stream. True eosinophils and basophils make up less than 0.1% of the total number of cells, and, when found, they have been classed with the neutrophils in this study.

In order to determine the cytologic response following the intraperitoneal injection of Bargaen's vaccine and of sodium ricinoleate, three groups of animals were used. Group 1 consisted of 20 animals which received injections of 5 cc. per kg. of body weight of a 1 to 160 solution of Bargaen's vaccine made up in sterile physiologic saline solution. Group 2 consisted of 10 animals which received 5 cc. per kg. of body weight of a 1% solution of sodium ricinoleate (likewise in physiologic saline solution); and Group 3 consisted of 10 animals which received a like amount of a 2% solution of sodium ricinoleate. Changes in the number of cells per cubic millimeter of peritoneal fluid and in percentage distribution of the different cells were recorded at intervals of 1, 3, 6, 12, 24, 48 and 72 hours and 1, 2 and 3 weeks. As with the control series, the data were treated statistically and the mean and its probable error were computed for each interval (Tables 1 and 2 and Fig. 1).

TABLE 1.—CELLS PER CUBIC MILLIMETER OF PERITONEAL FLUID.*

Time after injection.	Bargaen's vaccine.	1% solution of sodium ricinoleate.	2% solution of sodium ricinoleate.
1 hour	813 ± 109	2,000 ± 185	1,130 ± 165
3 hours	12,539 ± 878	13,720 ± 1,648	5,610 ± 554
6 "	47,775 ± 2,895	21,740 ± 2,105	12,580 ± 472
12 "	100,800 ± 10,141	30,490 ± 3,391	23,970 ± 2105
24 "	76,800 ± 9,484	40,050 ± 13,281	49,444 ± 3017
48 "	20,100 ± 1,885	24,110 ± 4,492	52,125 ± 4403
72 "	11,295 ± 1,620	26,450 ± 4,505	33,325 ± 5586
1 week	3,182 ± 279	8,977 ± 1,208	8,512 ± 624
2 weeks	1,347 ± 139	3,033 ± 262	5,206 ± 824
3 "	1,773 ± 158	2,133 ± 248	5,291 ± 1221

* Before injection, the number of cells per cubic millimeter was 1838 ± 65.

The cellular response to the intraperitoneal injection of all three solutions was found to be nearly identical qualitatively, although the maximal counts with the three solutions occurred at different time intervals, namely 12, 24 and 48 hours, respectively. The delay

TABLE 2.—PERCENTAGE DISTRIBUTION OF CELLS IN PERITONEAL FLUID.*

Time after injection.	After intraperitoneal injection of:					
	Bargen's vaccine.		1% solution of sodium ricinoleate.		2% solution of sodium ricinoleate.	
	Mono-cytes.	Neutro-phils.	Mono-cytes.	Neutro-phils.	Mono-cytes.	Neutro-phils.
1 hour . .	60.45 \pm 4.00	39.55 \pm 4.00	21.35 \pm 1.34	78.65 \pm 1.34	15.90 \pm 1.26	84.10 \pm 1.26
3 hours . .	2.36 \pm 0.33	97.64 \pm 0.34	4.15 \pm 0.33	95.85 \pm 0.31	5.45 \pm 0.69	94.55 \pm 0.69
6 " . .	8.05 \pm 1.04	91.95 \pm 1.05	11.80 \pm 0.85	88.20 \pm 0.85	5.20 \pm 0.79	94.80 \pm 0.79
12 " . .	19.18 \pm 1.55	80.82 \pm 1.66	20.05 \pm 0.72	79.95 \pm 0.72	18.50 \pm 2.22	81.50 \pm 2.22
24 " . .	30.44 \pm 2.52	69.56 \pm 2.52	41.00 \pm 3.92	59.00 \pm 3.92	29.88 \pm 2.21	70.12 \pm 2.17
48 " . .	72.31 \pm 1.52	27.69 \pm 1.52	92.80 \pm 1.06	7.20 \pm 1.06	65.69 \pm 3.93	34.31 \pm 3.93
72 " . .	94.22 \pm 1.12	5.78 \pm 1.12	95.05 \pm 1.91	4.95 \pm 1.91	93.62 \pm 1.30	6.38 \pm 1.29
1 week . .	98.94 \pm 0.19	1.06 \pm 0.17	99.70 \pm 0.11	0.30 \pm 0.11	97.63 \pm 1.30	2.37 \pm 1.40
2 weeks . .	99.58 \pm 0.24	0.42 \pm 0.24	98.55 \pm 0.58	1.45 \pm 0.58	99.00 \pm 0.33	1.00 \pm 0.33
3 " . .	99.59 \pm 0.06	0.41 \pm 0.11	99.39 \pm 0.26	0.61 \pm 0.28	99.75 \pm 0.08	0.25 \pm 0.08

* Before injection, the percentage of the monocytes was 99.45 \pm 0.07 and that of the neutrophils was 0.55 \pm 0.07.

in the return to normal levels following the use of sodium ricinoleate is undoubtedly attributable to the irritating qualities of this soap in the concentrations used. Indeed, injection of the 2% solution was found to be so irritating, as evidenced by shock 1 hour after injection in all of the 10 animals and by death of 2 animals from marked plastic peritonitis within 24 hours, that this strength solution has not been used since.

The changes in differential counts in all 3 instances were characterized by an immediate influx of neutrophils. The monocytes appeared much later and did not attain to the majority until the 48th hour.

Since the maximal cell count per cubic millimeter following the injection of Bargen's vaccine was approximately twice that which followed the use of sodium ricinoleate, one might be inclined to think that the former calls forth the better response. It must be remembered, however, that no true quantitative picture can be obtained from these data alone. Such a picture may be had only after determining the amount of peritoneal fluid. This was done by killing rabbits in groups of 5 at the designated hours following injection. By employing the technique of Seeley, Higgins and Mann, the abdomen was opened and the free fluid was mopped up with previously balanced filter papers (Table 3 and Fig. 2a).

TABLE 3.—WEIGHT OF PERITONEAL FLUID EXPRESSED IN GRAMS PER KILOGRAM OF BODY WEIGHT.*

Time after injection.	After intraperitoneal injection of:	
	Bargen's vaccine.	1% solution of sodium ricinoleate.
1 hour	2.598 \pm 0.35	
3 hours	2.170 \pm 0.26	
6 "	2.830 \pm 0.36	5.156 \pm 0.35
12 "	1.380 \pm 0.19	7.390 \pm 1.49
24 "	1.212 \pm 0.22	4.240 \pm 0.62
48 "	3.158 \pm 0.53	2.720 \pm 0.10
72 "	1.700 \pm 0.14	4.430 \pm 0.55
1 week	1.850 \pm 0.42	1.876 \pm 0.60

* Before injection, the weight was 1.244 \pm 0.14.

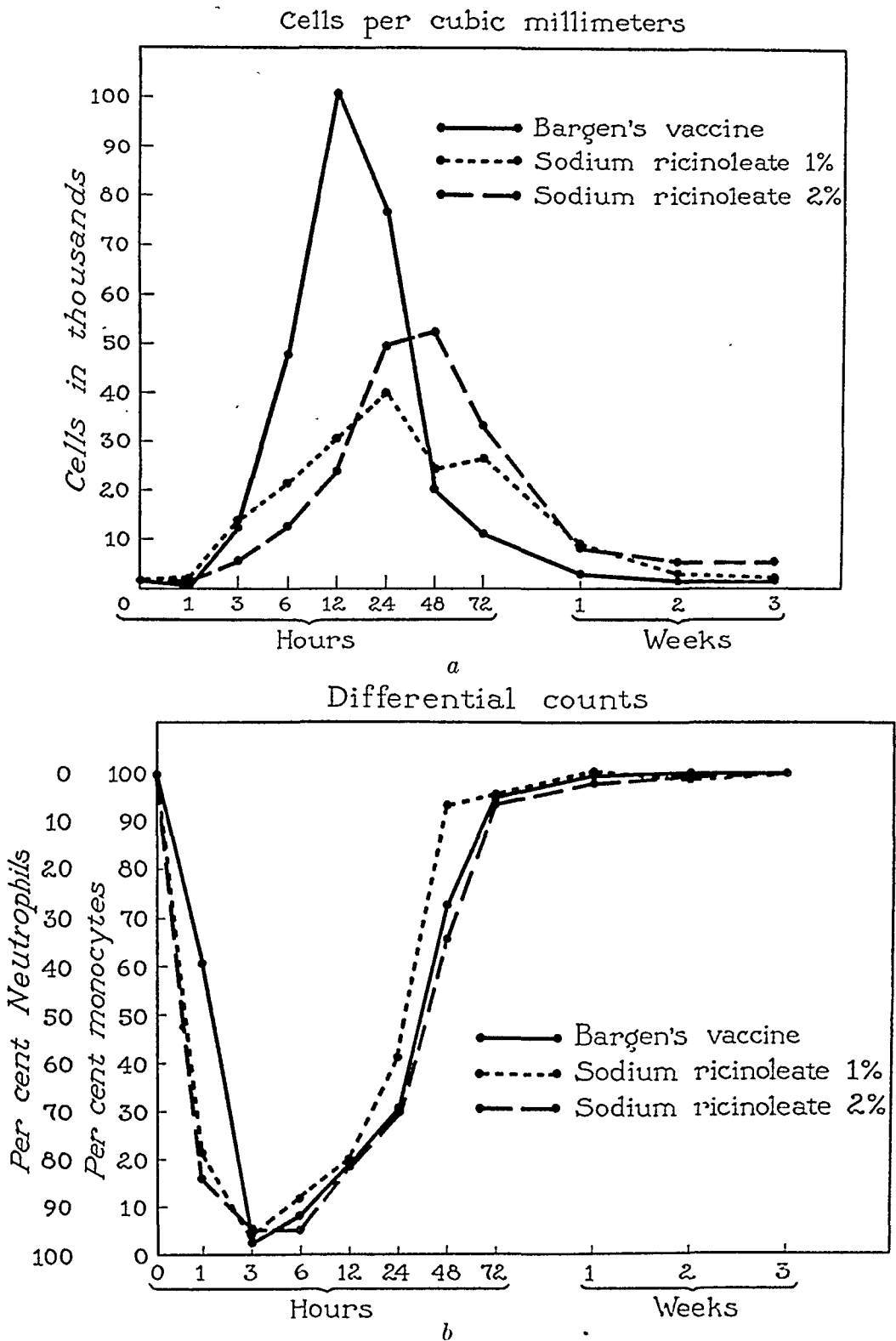
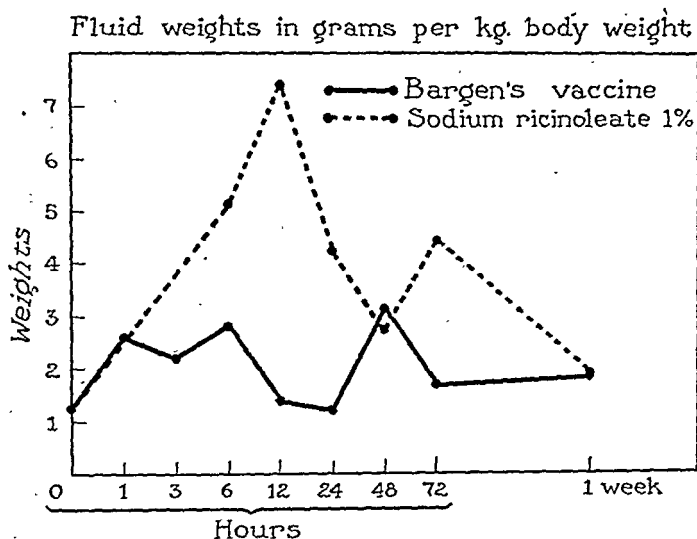
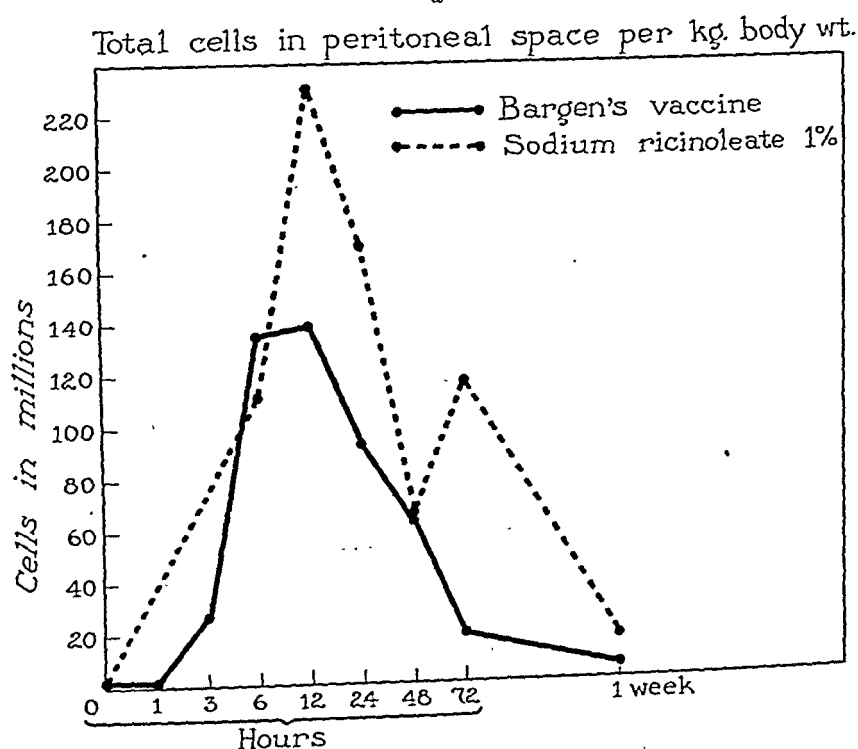


FIG. 1.—*a*, Changes in the number of peritoneal cells per cubic millimeter following the intraperitoneal injection of Bergen's vaccine and solutions of sodium ricinoleate; *b*, changes in the percentage distribution of the peritoneal monocytes and neutrophils following the intraperitoneal injection of Bergen's vaccine and solutions of sodium ricinoleate.



a



b

FIG. 2.—*a*, Changes in weight of peritoneal fluid following the intraperitoneal injection of Bargen's vaccine and 1% solution of sodium ricinoleate; *b*, changes in the total number of cells in the peritoneal space following the intraperitoneal injection of Bargen's vaccine and 1% solution of sodium ricinoleate.

Knowing the number of cells per cubic millimeter and the fluid weights, the total number of cells in the peritoneal space per kilogram of body weight could then be calculated (Fig. 2b).*

It will now be seen that the cytologic response to the intraperitoneal injection of sodium ricinoleate is greater than is the response to the injection of Bargen's vaccine. The total number of neutrophils and monocytes at the stated intervals have likewise been computed (Fig. 3). It is demonstrated very nicely by this means

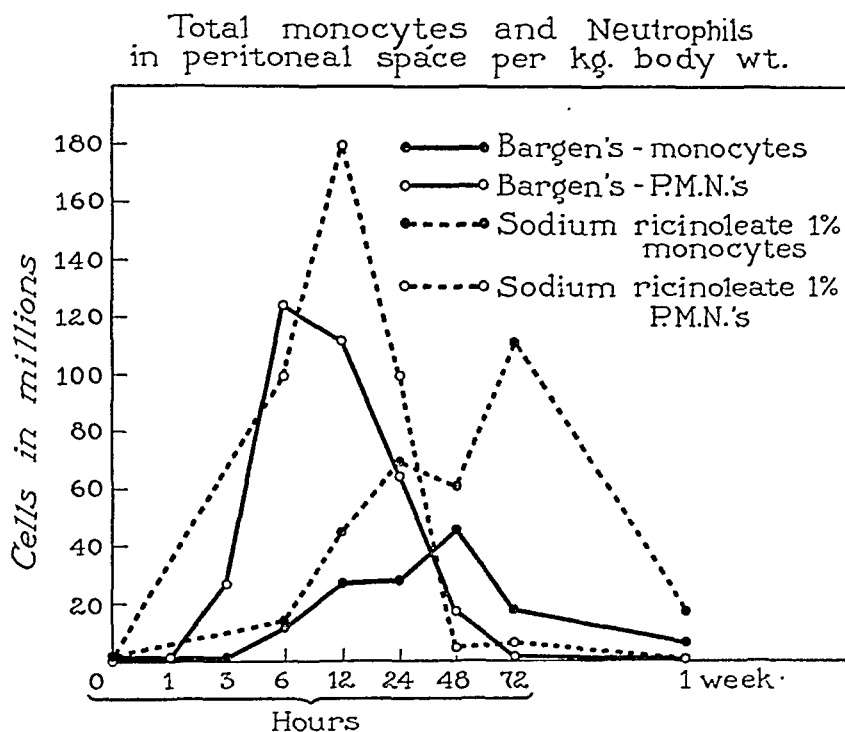


FIG. 3.—Changes in the total number of monocytes and neutrophils in the peritoneal space following the intraperitoneal injection of Bargen's vaccine and 1% solutions of sodium ricinoleate.

that, if the monocyte is the truly important cell in the production of the local protection to the peritoneum, certain of the workers mentioned earlier in this paper are correct in making injections 1 to 3 days prior to operation. There is still, however, considerable controversy over the question of the proper time for making the injections. Some prefer to make them 6 to 12 hours before the operation and thus operate at a time when the neutrophils are present in the greatest abundance. There is as yet no convincing evidence that the "local protection" is at a maximum when the

* It is, of course, realized that the weight of 1 cc. of peritoneal fluid will vary with the number of cells, and amount of fibrin content in the fluid. For the sake of convenience in calculating these values, I have taken 1 cc. as being equivalent to 1 gm.

monocytes are most numerous. Future work will no doubt clear up the question of the relative importance of the two general types of peritoneal cells.

Comment. Recent developments in the prophylaxis of post-operative peritonitis by means of preoperative intraperitoneal injections of various substances, vaccinal and otherwise, have convincingly reduced its mortality. This seems to have been accomplished largely by the production of a local protection to the peritoneum, which is attributable to a local hyperleukocytosis. In all probability any of a large number of substances, specific and non-specific, will be found to be equally effective. Good results with each will depend on finding the optimal concentration and quantity of that substance which, when injected, will be maximally stimulating without being irritating. More extensive investigation is now being undertaken in an attempt to discover that optimum for Barger's vaccine and for sodium ricinoleate.

Future advances in the prophylaxis and treatment of peritonitis will undoubtedly be made through the investigation of specific serums and vaccines, and of certain substances which, like sodium ricinoleate, are known to be detoxifying and bactericidal.

Summary. In the study of peritoneal immunization one is concerned with a true immune process and a local protection to the peritoneum which is afforded by local hyperleukocytosis. The cellular response in the peritoneum of the rabbit has been studied at specified intervals following the intraperitoneal injection of Barger's vaccine and solutions of sodium ricinoleate. The data presented represent average cell counts per cubic millimeter, differential counts and total cell counts. Attention is called to the fact that the cytologic responses to the two substances are qualitatively nearly identical. This qualitative similarity of response has been found following the injection of any of a large number of vaccines and other substances.

I am indebted to the William S. Merrell Company for supplying the sodium ricinoleate (Soricin-Surgical) used in this study.

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EFFECT OF ENCEPHALOGRAPHY ON BLOOD SUGAR LEVEL OF CHILDREN.

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(From the Emma Pendleton Bradley Home.)

THE fact that the central nervous system may influence carbohydrate metabolism has been repeatedly demonstrated since Claude Bernard first produced *piqûre* diabetes in 1849. More specifically, it has been noted that such physical changes as cranial trauma⁶ and conditions producing alterations of intracranial pressure¹⁸ may affect glucose tolerance and blood sugar levels. However, in spite of the wide diagnostic use of lumbar puncture and pneumo-encephalography, both directly producing changes in cerebrospinal fluid pressure, few reports of their effect on the blood sugar level have been published. Mader,^{13a,b} in 1928, first reported that after encephalography the blood sugar becomes temporarily elevated, and Schönfeld,¹⁶ in 1933, stated that there was a consistent brief rise in blood sugar level following diagnostic lumbar puncture in children. Boeters,² in 1935, reported observations similar to those of Mader though he does not refer to this earlier work. There have been as yet no reported observations of such changes in the English literature.

This subject came to our attention while we were comparing fasting glucose levels in the spinal fluid and blood of children. In a few patients the blood specimen was by chance taken very shortly after encephalography had been performed. The blood sugar values in these cases were found to be unusually high, although subsequent fasting blood sugar levels in the same children were within normal limits. Such observations led us to this study of the response of blood sugar level to encephalography.

Material. As the Emma Pendleton Bradley Home is devoted exclusively to the care of children with neurologic and behavior disorders, all studies were upon patients of this type. Inasmuch as there were clinical indications for encephalography in each patient included in this study, these children can scarcely be classified as "normal, healthy subjects." However, in none of the patients discussed in this paper was the spinal fluid itself or its pressure relationships actually found to be pathologic. We have included no patients in whom there was any evidence of endocrine or other metabolic disorder. Examination was made upon 15 patients under fasting

conditions (12 to 17 hours after the last previous meal) usually about 3 hours after awakening in the morning.

Methods. In the first 10 patients (Table 1) venous blood was analyzed for glucose content by the method of Lewis and Benedict.¹² This procedure gives readings somewhat higher than methods subsequently used. As we were observing fluctuation of glucose level in individual patients and in no sense measuring absolute values, this discrepancy seems irrelevant. All venous blood samples were drawn into a clean dry syringe from the internal jugular vein or median basilic or cephalic veins of the forearm. The blood was immediately transferred to a stoppered test tube containing a few crystals of potassium oxalate to prevent coagulation, and the tube then gently inverted a few times to insure mixture. No known clotted samples were analyzed. The precipitation of proteins was carried out within one-half hour and all these analyses were performed by one individual (R. V. H.).

In the last 5 patients (Table 1) who were studied somewhat more closely, capillary blood sugar values were determined by the colorimetric ferricyanide method of Folin.⁸ In these children blood samples were taken before pre-operative medication and anesthesia, following medication and anesthesia but before encephalography, at 3-minute intervals during encephalography, and at $\frac{1}{2}$ - and 1-hour intervals following the procedure. The results of these analyses are graphically presented in Chart I. Except for the 3-minute samples during encephalography, these capillary blood determinations were carried out and checked in duplicate, and were performed by one individual (R. M. C.).

Spinal fluid glucose content was determined in Patients 1 to 12 by the method of Lewis and Benedict¹² and in Patients 13 to 15 by the Folin-Wu technique.⁹

Time relationships for all the shorter intervals were measured with a standard stopwatch.

Effect of Encephalography Upon Blood and Spinal Fluid Sugar.
Encephalography Procedure. We use the term "encephalography" as commonly accepted to mean roentgenography of the skull following the withdrawal of cerebrospinal fluid and its replacement by air. This replacement is done by means of lumbar puncture with the patient in the sitting position. We employ the multiple syringe method advocated by Davidoff and Dyke⁵ and others. An attempt was made to completely drain the spinal fluid and replace it with an equal or slightly greater amount of air. Following fluid replacement, roentgenograms of the skull were taken in various positions, necessitating some manipulation of the patient. The child was then put to bed in the prone position for the following 24 hours.

Some form of general anesthetic was used in all cases. This was usually avertin, given rectally $\frac{1}{2}$ hour before operation, always in doses of 100 mg. per kg. body weight. This was occasionally preceded by morphine sulphate, gr. $\frac{1}{8}$ to $\frac{1}{6}$, and atropine sulphate, gr. $\frac{1}{200}$, both given hypodermically. When additional anesthesia was necessary, light ether for 10 to 20 minutes by inhalation (Cases 3 and 7) or 2 to 4 cc. of paraldehyde intravenously (Cases 12 and 15) was used.

Blood Sugar Response. Observations of the blood sugar level in association with encephalography were made upon 15 patients from 8 months to 12 years of age between July, 1933, and December, 1935 (Table 1). It will be observed that the blood sugar level fol-

lowing encephalography was either at an abnormally high level or showed a distinct increase over that noted before the procedure. Fasting specimens taken before encephalography or at previous observation showed values over the normal range in all cases.

TABLE 1.—RESPONSE OF BLOOD GLUCOSE TO ENCEPHALOGRAPHY.

Pt.	Date.	Sex.	Age, yrs.	Diagnosis.	Anesthetic	Fluid removed, cc.	Air injected, cc.	Blood sugar, mg. %.			Rise.
								Previous fasting.	Just before enceph.*	After enceph.†	
1	7/18/33	M	7	Convulsive	Avertin	72	72	126	..	200	
2	11/14/33	F	12	Convulsive	Phenobarbital Sodium amytal	130	130	102	..	182	
3	4/13/34	F	5½	Convulsive	Avertin Ether	85	85	111	..	200	
4	5/17/34	M	3½	? posten- cephalitic	Avertin	125	125	66	..	200	
5	8/21/34	M	8½	Cerebral agenesis	2 cc. paraldehyde	65	65	222	
6	10/ 4/34	M	12	Convulsive	½ oz. paraldehyde	80	80	102	109	222	113
7	10/ 5/34	F	10	Convulsive	Avertin Ether	80	80	93	103	187	81
8	2/ 8/35	F	11	Convulsive	Avertin Morphine Atropine	95	120	116	91	232	141
9	2/ 9/35	F	10	Convulsive	Avertin Morphine Atropine	92	115	111	116	167	51
10	4/12/35	M	11	Convulsive	Avertin Morphine Atropine	70	85	93	81	235	151
11	8/20/35	M	12	Convulsive	Avertin Morphine Atropine	110	140	89	94	136	42
12	8/29/35	M	5	Convulsive	Avertin Morphine Atropine Paraldehyde	70	90	96	137	177	40
13	10/25/35	M	6	Hemiplegia Convulsive	Avertin Morphine Atropine	60	70	118	113	192	79
14	12/10/35	F	10	Convulsive	Avertin Morphine Atropine	72	90	110	112	165	53
15	12/12/35	F	7	Convulsive	Avertin Morphine Atropine Paraldehyde	69	98	100	131	209	75

* Specimens taken 30 to 45 minutes after complete anesthesia, 5 to 15 minutes before initial lumbar puncture.

† All specimens taken 30 to 60 minutes after initial lumbar puncture.

‡ Months.

The blood samples showing hyperglycemia were taken shortly after completing roentgenography. This was usually 30 to 60 minutes after spinal fluid replacement had been started and 15 to 20 minutes after it had been completed, the variation depending on the technical difficulties encountered.

Patient 5, on whom no fasting blood sugar determination was made during his stay in the hospital, at no time showed clinical evidence of hyperglycemia or related conditions.

From the data presented, it is evident that there exists no obvious relationship between the hyperglycemia produced in any case and the patient's sex, age, clinical diagnosis, the anesthetic employed,

the amount of spinal fluid withdrawn, air injected, or the previous fasting blood sugar level. The encephalograms were essentially negative with the exception of 3 (Patients 4, 5 and 10) who showed moderate non-localized "cortical atrophy," and 2 (Patients 13, 15) showing unilateral cerebral atrophy.

Encephalography Blood Sugar Curves. In 5 of these patients (Cases 11 to 15) blood sugar determinations were made at frequent intervals before, during and after encephalography. The resulting curves are shown in Chart I. It will be noted that anesthesia itself

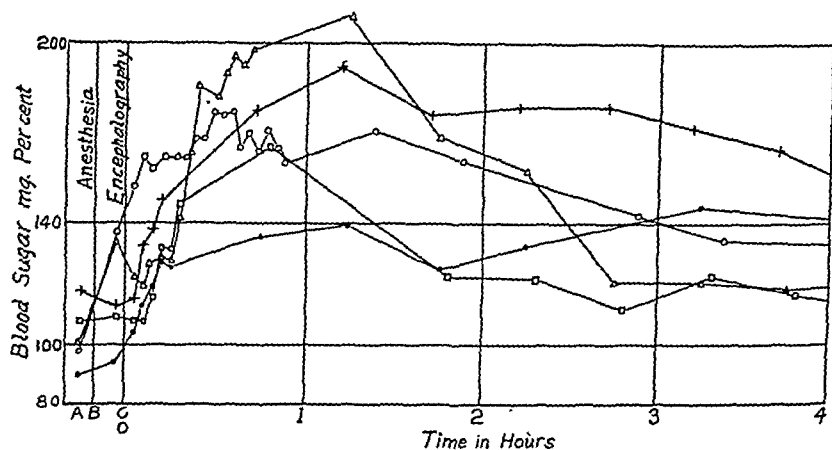


CHART I.—Blood sugar curve associated with encephalography in 5 children. A, Pre-anesthetic fasting blood sugar; B, point of administration of pre-operative drugs and anesthetic; C, cerebrospinal fluid replacement started. ●, Patient 11; O, Patient 12; +, Patient 13; □, Patient 14; △, Patient 15. Capillary blood sugar values are recorded. Duration of fluid replacement is indicated in each case by the very frequent (3-minute) samples taken during the procedure. This chart demonstrates the rapid rise and slow fall of blood sugar, which is in point of time associated with the air injection, rather than any anesthetic used.

produced little change in sugar level but that hyperglycemia began to appear immediately during fluid replacement with a peak reached 30 to 60 minutes after starting the procedure. The type of fall in blood sugar level varied but was much slower than the rise.

Spinal Fluid Sugar During Encephalography. In 5 children (Cases 8, 9, 11, 13, 14) serial blood-free samples of spinal fluid as removed fractionally during encephalography were analyzed for glucose content. No progressive or otherwise significant alterations in the glucose level beyond the limits of error for the method were noted in any of these cases. There was no valid evidence of any immediate reflection of the increased blood sugar in these individuals.

Comment. Our observations on children corroborate and amplify the reports of Mader^{13b} and Boeters² regarding elevation of blood sugar following encephalography.

Mechanism Producing Hyperglycemia. Although consistent elevation of blood sugar after encephalography appears to be an established fact, the mechanism producing this response is conjectural.

Tychowski and Crowell¹⁸ suggest that temporary alterations in pressure of the cerebrospinal fluid about the brain may mechanically stimulate "centers" in the central nervous system, thus initiating physiologic changes producing hyperglycemia. Mader^{13a,b} felt that introduction of a foreign substance (air) to the cerebrospinal system served as a stimulant by irritation. Boeters,² who also noted changes in temperature, pulse rate and leukocyte count suggests that encephalography stimulates nuclei in the diencephalon, producing a general sympathetic discharge. Schönfeld,¹⁶ who constantly observed similar though less marked blood sugar findings in children following the withdrawal of spinal fluid at simple lumbar puncture, implies that mere withdrawal of the fluid provides such a stimulus.¹¹

Measurement of Pressure Changes. Although we suspect that cerebrospinal fluid pressure changes about the brain may be one of the essential mechanisms initiating the blood sugar rises we observed, the pressure readings are not included upon our patients in this report. These were omitted because we feel that in using the method and clinical material at our disposal our pressure data are unreliable. As far as encephalography is concerned it is known that pressure relationships around the brain are not measured by the open manometer at the lumbar level when the patient is in the sitting position. Here we are recording to a large extent pressure exerted by the vertical column of fluid in the spinal canal. The recent work of von Storch^{17a} and others demonstrates that volume-for-volume replacement of fluid by air does not necessarily assure constant intracranial pressure. Possibly the use of a closed system of fluid replacement with special pressure controlling devices as employed by Piercy¹⁵ and by von Storch^{17b} may make possible pressure records which would be significant in studies such as the present.

Effect of Anesthetic. The effect of anesthesia upon our observations during encephalography merits consideration. Most of the anesthetics used upon our patients (Table 1) are known to exert some influence upon carbohydrate metabolism. Avertin^{19a,b,10} and ether^{7,1,3,14,4} have been especially studied, but in the doses we employed they do not affect the human blood sugar to the degree that we observed. Inasmuch as we employed several drugs affecting the blood glucose level in various ways, yet uniformly obtained hyperglycemia in encephalography, we may assume that the effect of drugs upon the hyperglycemia was not very striking. Chart I graphically demonstrates that in 5 cases real hyperglycemia followed spinal fluid replacement rather than the administration of the anesthetic. Cases 12 and 15 who were given paraldehyde showed a mild rise in the sugar level before encephalography was actually started.

Effect of Roentgenography. Chart I also demonstrates that the blood sugar begins to rise during fluid replacement, before that portion of encephalography involving the use of Roentgen rays is

carried out. Therefore, we have no reason to assume that exposure to Roentgen rays plays a part in the phenomenon. Boeters² studied the blood sugar before and after routine skull films were taken, and observed no significant changes.

Conclusions. 1. Encephalography as commonly carried out in children consistently results in hyperglycemia, with blood sugar levels often in the vicinity of 200 mg. %.

2. The blood sugar rises rapidly during spinal fluid replacement, reaches its peak within an hour and falls over a period of several hours.

3. Hyperglycemia following encephalography bears no obvious relationship to anesthetic used, the clinical condition or age of the child studied, the amount of fluid withdrawn or air injected.

4. The physiologic explanation of the mechanism producing this hyperglycemia is still in a theoretical stage.

5. There is no evidence that encephalography hyperglycemia is reflected by an increase in cerebrospinal fluid glucose sufficiently promptly to be demonstrated in samples taken during the operation.

6. Studies of the blood sugar level in association with encephalography should be carried out with the above conclusions in mind.

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FAILURE OF CALCIUM THERAPY TO DIMINISH SUGAR EXCRETION IN RENAL GLYCOSURIA.

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THE impression is gained from medical literature that the renal permeability for dextrose may be altered by the administration of calcium. Cammidge³ states that in renal glycosuria the blood calcium is often diminished and when calcium and parathyroid

extract are given by mouth to such patients the excretion of dextrose in the urine is decreased. Although it is generally conceded that renal glycosuria is a harmless anomaly, some cases have been diagnosed erroneously as diabetes mellitus and low carbohydrate diets prescribed, with the result that ketosis has occasionally supervened. Some specific agent, such as calcium or parathormone, which would tend to decrease or abolish the excretion of dextrose, would prove to be a valuable therapeutic asset in the treatment of this condition, and particularly in cases of diabetes mellitus with low renal thresholds.

The present report is based on studies made over a period of 181 hours on the rate of dextrose excretion in the urine, before, during and after the simultaneous administration of calcium gluconate and parathormone in a male child with renal glycosuria. The boy was 3 years old at the time this particular study was carried out.

Case Report. L. F., male, aged 3, was first admitted to the Pediatric Wards of this hospital on November 19, 1931, during an attack of acute bronchitis, tonsillitis and pharyngitis. Six months prior to admission, a diagnosis of diabetes mellitus was made elsewhere on the basis of glycosuria. The patient was born at term; normal labor; moderate asphyxia; birth weight $5\frac{1}{4}$ pounds; mental and physical development normal. The family history was irrelevant.

Physical examination: weight, 32 pounds. Examination essentially negative except for tonsillitis and pharyngitis. Mantoux test negative. Urine sugar varied from 0.5 to 5%. Urine acetone was 3+ for the first few days. A dextrose tolerance test was essentially normal (Table 1). Blood Wassermann negative. Plasma carbon dioxide was 35 volumes %; otherwise the blood chemistry was normal. A blood count showed moderate secondary anemia. The urine sugar was identified as dextrose by the phenylhydrazin test. Discharged December 1, 1931. Diagnosis: renal glycosuria with considerable excretion of dextrose and development of an acidosis during an intercurrent infection while on a restricted carbohydrate intake.

Second admission (February 25 to 27, 1932) for tonsillectomy and adenoidectomy. Urine sugar, 3.4%. Urine acetone, negative. *Third admission* (May 12 to 21, 1932) for special study. *Fourth admission* (October 23 to 27) for complaints of abdominal cramps, history of convulsions and temperature of 104° F. Urine sugar varied from 1 to 1.4%. Urine acetone negative. Roentgen ray of the skull showed the coronal suture to be a shade prominent; the sella turcica was within the average normal size and variations; no evidence of increased intracranial pressure or of erosions. Blood chemistry normal. Blood count improved.

Fifth admission (October 17 to 20, 1934) with complaints of abdominal pain and temperature of 105° F. History of a fainting spell. Urine sugar varied from 2 to 4%. Urine acetone negative to 1+. Roentgen ray of the skull negative. Blood chemistry and blood count normal.

Sixth admission (November 6 to 10, 1935) for special study. Urine sugar, 2.85%. Urine acetone, negative. Blood chemistry and blood count, normal. A dextrose tolerance test was essentially normal (Table 1).

Special Study. Figure 1 shows the results obtained during the experimental period of observation. The excretion of dextrose in the urine, determined over a period of 72 hours with the patient on a uniform diet, varied from 0.4 to 2.2 gm. per hour. A dextrose

TABLE 1.—THE RESULTS OF TWO DEXTROSE TOLERANCE TESTS CARRIED OUT FOUR YEARS APART IN THE CASE OF RENAL GLYCOSURIA CITED IN THIS PAPER.

Date.	Dextrose ingested,* gm.	Blood sugar (mg. %).			Urine sugar (gm. %).		
		Control.	1 hr.	2 hrs.	Control.	1 hr.	2 hrs.
11/24/31	25.4	96	112	108	0.35	0.25	0.20
11/ 7/35	41.0	80	110	90	4.00	4.80	4.80

* 1.75 gm. of dextrose per kg. of body weight.

tolerance test revealed a normal curve with a low renal threshold for dextrose. Simultaneous serum calcium determinations revealed high figures, but probably within the normal range; however, a moderate reduction in serum calcium followed the dextrose ingestion (Fig. 1). The effect of increasing concentrations of serum calcium

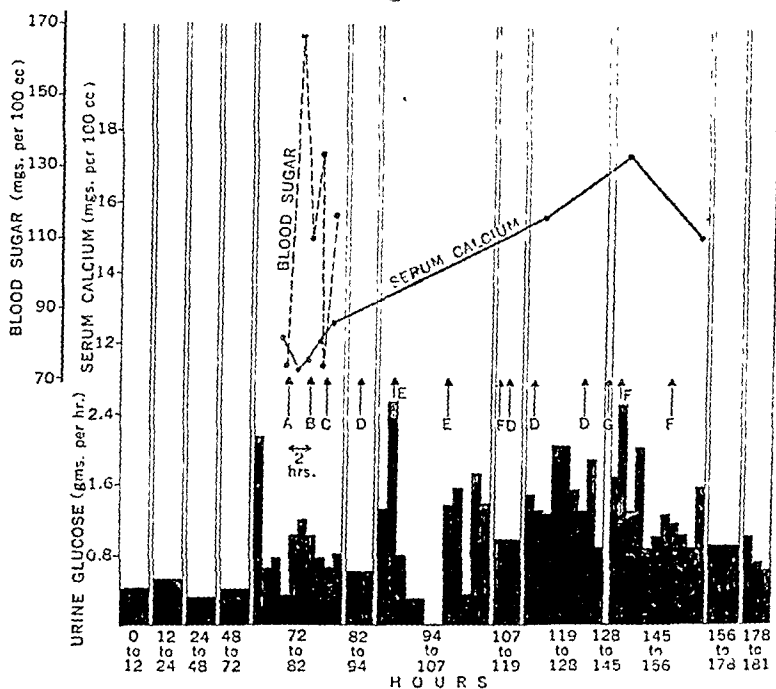


FIG. 1.—The effect of induced hypercalcemia on the dextrose excretion in the urine in a case of renal glycosuria. A, 1.75 gm. of glucose per kg. by mouth. B 1.75 gm. of glucose per kg. by mouth and 7.5 cc. of 10% calcium gluconate intramuscularly. C, 7.5 cc. of 10% calcium gluconate intramuscularly. D, 20 units of parathormone intramuscularly. E, 15 units of parathormone intramuscularly. F, 10 units of parathormone intramuscularly. G, 20 units of parathormone intramuscularly in two divided doses 6 hours apart.

upon the rate of sugar excretion in the urine was then studied. Calcium gluconate, employed for this purpose, appeared to be ineffective in influencing the serum calcium appreciably. Consequently, parathormone was substituted. Following 100 units of parathormone intramuscularly over a period of 24 hours, the serum calcium rose to 15.6 mg. %. During this period there appeared to be a moderate increase in the rate of dextrose excretion in the urine. The parathormone was continued for another 24 hours, during

which period 60 units were administered intramuscularly. At this time the serum calcium had increased to 17.4 mg. % and vomiting ensued. This marked hypercalcemia appeared to exert little or no influence on the renal excretion of dextrose.

The whole blood sugar was determined by the method of Folin and Wu⁶; serum calcium by the Clark-Collip⁵ modification of the Kramer-Tisdall method; urine sugar by Benedict's¹ procedure. The blood specimens were obtained by puncture of the external jugular vein.

Discussion. Our present concepts concerning the functional pathology of proteinuria and glycosuria would lead us to believe that the former alone may be considered as due to increased renal permeability; in these cases (functional or orthostatic albuminuria) calcium therapy has had some measure of success (Burden⁵). The effectiveness of this form of therapy in orthostatic albuminuria is probably due to the inhibitory effect exercised by the calcium ion on the permeability of the cell membrane (Cantarow⁴). Renal glycosuria, however, does not represent increased filtration of dextrose in the glomerular tuft, but rather diminished ability of the kidney tubules to resorb the filtered sugar completely. The rationale for calcium therapy in this condition is not as clear as is its use in the functional albuminurias.

Cambridge,³ Labbé⁸ and Hetényi⁷ have reported that calcium therapy, especially a combination of calcium feeding and parathormone injections or parathyroid extract by mouth, is effective in diminishing the rate of the dextrose excretion in renal glycosuria. The present report, based on a single proven case though studied in some detail, fails to show such an effect. In fact, the marked hypercalcemia (17 mg. %) was not accompanied by any noteworthy changes in the rate of dextrose excretion. Wiener⁹ has had a similar negative result with the use of parathormone in a case of renal glycosuria.

Conclusion. A case of renal glycosuria, observed for 5 years, showed no impairment in carbohydrate tolerance. Despite a fairly constant normal level of blood sugar, marked fluctuations in the rate of sugar excretion in the urine occurred.

Contrary to some observations cited in the European literature, the administration of calcium gluconate and parathormone, resulting in a marked elevation of serum calcium, exerted little or no effect on the rate of sugar excretion in the urine.

Through the courtesy of Dr. Adolph G. DeSanctis, this case was studied on the wards of the Pediatric Service.

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BOOK REVIEWS AND NOTICES.

ROENTGEN INTERPRETATION. A Manual for Students and Practitioners. By GEORGE W. HOLMES, M.D., Roentgenologist to the Massachusetts General Hospital and Clinical Professor of Roentgenology, Harvard Medical School, and HOWARD E. RUGGLES, M.D., Roentgenologist to the University of California Hospital and Clinical Professor of Roentgenology, University of California Medical School. Pp. 356; 243 illustrations. Fifth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, \$5.00.

This manual for students and practitioners is an excellent, brief survey of the field of Roentgen ray diagnosis. It is designed to cover the essentials of the subject, which it does admirably well. This edition is beautifully illustrated, and the subject matter clearly described. The authors have added considerably to the chapters on Bone Pathology and the Chest. Some of the recent advances in gastro-enterology are also discussed. While the book will find its greatest use in the hands of physicians other than radiologists, it has its place in the radiologist's library because of its illustrations and bibliography.

P. H.

DISINFECTION AND STERILIZATION. By ERNEST C. McCULLOCH, M.A., D.V.M., Ph.D., Biological Research, Pennsylvania Salt Manufacturing Company, etc. Pp. 525; 53 illustrations and 232 tables. Philadelphia: Lea & Febiger, 1936. Price, \$5.50.

THE 19 chapters in this volume start with "The Development of Our Knowledge of Disinfection and Sterilization" and end with "The Selection of a Disinfectant." The scope is indeed comprehensive. Not only are the natural agencies which control microbial populations discussed, but the germicidal properties of the body, the effect of radiant energy emanations, temperature and other physical agents, on bacterial growth are fully and clearly discussed. The usefulness of heavy metals, dyes, the phenols and halogens is reviewed. This volume will be of use not only to bacteriologists in medicine and in industry, but also to students, practitioners and public health workers. In fact, in the entire field of human endeavor where sterilization and disinfection are concerned, this book will fulfil the need. Each chapter ends with an excellent bibliography. The facts are presented clearly and the discussion is presented in the form which makes it interesting. A wealth of material is covered in the 525 pages. The index is excellent.

I. R.

TREATMENT IN GENERAL PRACTICE. The Management of Some Major Medical Disorders. I. Articles Republished from the *British Medical Journal*. Pp. 250. New York: Paul B. Hoeber, Inc., 1936. Price, \$3.50.

SINCE December, 1934, the *British Medical Journal* has been publishing each week one of a series of articles on treatment, contributed at the editor's invitation by teachers of clinical medicine, subject and author being chosen from the viewpoint of appropriateness. These are now being reprinted in a series of medium-sized volumes for greater accessibility. The present volume contains the first 35 articles, 14 dealing with certain diseases of the respiratory tract, 6 on acute infections and 15 on cardiovascular diseases. The topics selected cover a limited but important field of medical practice. The presentations are of a high order of excellence and eminently practical. The general practitioner should find this a very helpful book.

R. K.

PATHOLOGICAL PHYSIOLOGY AND CLINICAL DESCRIPTION OF THE ANEMIAS. By WILLIAM BOSWORTH CASTLE, M.D., S.M. (HON.), Associate Professor of Harvard University; Associate Director, Thorndike Memorial Laboratory and Junior Visiting Physician, Boston City Hospital, and GEORGE RICHARD MINOT, M.D., S.D. (HON.), F.R.C.P., EDIN. (HON.), Nobel Laureate in Medicine, 1934; Professor of Medicine, Harvard University; Director, Thorndike Memorial Laboratory and Visiting Physician, Boston City Hospital. Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (HON.), Hersey Professor of the Theory and Practice of Physic, Harvard University; Physician-in-Chief, Peter Bent Brigham Hospital, Boston. Pp. 205. New York: Oxford University Press, 1936. Price, \$3.00.

THIS is not a textbook on hematology, nor is much space devoted to diagnostic methods and there are no illustrations. This is not said in criticism of the work but to inform the readers of this review. However, the book does full justice to its title. In the past decade our knowledge concerning the anemias, as a result of the discovery by Minot and Murphy of the curative effect of liver feeding in pernicious anemia, has seen the greatest advances in its history, advances to which the authors and their associates have continued to make numerous and valuable contributions. No one is therefore better qualified than the authors to state our present knowledge of the pathologic physiology, clinical manifestations and treatment of the anemias. Written first as a section in Oxford Loose-Leaf Medicine, it now appears as this separate volume so that it may be more generally available. The book is highly recommended to all practitioners of medicine. R. K.

YOUR HAY FEVER. By OREN C. DURHAM, Chief Botanist, Abbott Laboratories, North Chicago, Ill. With an Introduction by MORRIS FISHBEIN, M.D., and a Chapter on Treatment by SAMUEL M. FEINBERG, M.D., F.A.C.P. Pp. 264; 17 illustrations and 7 tables. New York: The Bobbs-Merrill Company, 1936. Price, \$2.00.

THE story of what has been accomplished in discovering the causes and prevention of hay fever, told for the layman in an accurate and entertaining manner by a man eminently qualified to tell the story. Since one American in every fifty has hay fever, the book should have a wide appeal. R. K.

PARENTERAL THERAPY. A Ready Reference Manual of Extra-Oral Medication for Physicians, Dentists, Pharmacists, Chemists, Biologists, Nurses, Medical Students and Veterinarians. By WALTON FOREST DUTTON, M.D., Formerly Medical Director, Polyclinic and Medico-Chirurgical Hospitals, Graduate School of Medicine, University of Pennsylvania, etc., and GEORGE BURT LAKE, M.D., Formerly Special Lecturer in Hygiene, Purdue University, etc. Pp. 376; 90 illustrations. Springfield, Ill.: Charles C Thomas, 1936. Price, \$7.50.

WHILE this book undoubtedly contains information that is useful and practical, its authors have committed the error of spreading their work over so much territory that it has in many places become exceedingly thin. How many physicians would need to know the technique for an alcohol injection into the Gasserian ganglion? Yet the doctor cannot find details of hay fever treatment. The therapeutic index is so abbreviated (in order to be able to mention great numbers of proprietaries) as at times to be dangerous: e.g., "*Auricular fibrillation*: Quinidine sulphate, intravenously to ameliorate or stop attack"—yet there is no mention of quinidine in the index or "pharmacologic notes" where drug actions, contraindications, etc., are considered. The book is not recommended. R. K.

AN INDEX OF TREATMENT. By various writers. Edited by ROBERT HUTCHINSON, M.D., LL.D., F.R.C.P., Consulting Physician, London Hospital, and Hospital for Sick Children, Great Ormond Street. Pp. 1020; 147 illustrations. Eleventh edition, revised. Baltimore: William Wood & Co., 1936. Price, \$12.00.

THIS is an excellent book. Here, alphabetically arranged, in a single volume is found material that one would have to dig out of a dozen books on medicine, surgery, and the specialties. It is the work of 91 contributors, selected because of their special experience. Nothing further need be said in praise of a book that has reached its eleventh edition in 29 years.

R. K.

SYNOPSIS OF DISEASES OF THE HEART AND ARTERIES. By GEORGE R. HERRMANN, M.D., PH.D., Professor of Clinical Medicine, University of Texas, etc. Pp. 344; 88 illustrations and 3 color plates. St. Louis: The C. V. Mosby Company, 1936. Price, \$4.00.

IN the words of the author this book "... is in no sense of the word a book for the specialist, but is intended primarily for the plodding student and the assiduous conscientious practitioner." The first five chapters describe the clinical and laboratory methods commonly employed in the study of heart disease. The sixth chapter elaborates upon a familiar classification of diseases of the heart. In the remaining 200 pages are short chapters dealing with disorders of cardiac mechanism, the diagnosis and treatment of heart failure according to its various causes, and a very brief discussion of diseases of arteries. The author has rightly attempted to present his field in the light of pathologic physiology, in order that the "plodding student" shall not be content with committing to memory the physical signs of heart disease. The introductory chapters are excellent and meaty. However, the volume of material discussed does not allow for sufficient emphasis of the most important considerations. The presentation of the various types of heart disease according to etiology could be shortened by 50 pages without loss of emphasis. To the intent reader the constant repetition is only tiresome. Therapy is described succinctly. Perhaps the uninitiated would benefit from a word of caution about some of the drugs recommended, *e.g.*, acetyl-beta-methyl choline. The organization of material, while suited for reference by the practitioner, probably will not serve to orientate the medical student so well as other books more simply written.

W. J.

EXOPTHALMIC GOITER AND ITS MEDICAL TREATMENT. By ISRAEL BRAM, M.D., Medical Director, Bram Institute for the Treatment of Goiter and Other Diseases of the Ductless Glands, Upland, Pa., etc. Foreword by R. G. HOSKINS, PH.D., M.D., Director of Research, Memorial Foundation for Neuro-Endocrine Research, Harvard Medical School, Boston. Pp. 456; 79 illustrations. Second edition, completely revised and enlarged. St. Louis: The C. V. Mosby Company, 1936. Price, \$6.00.

THE first 250 pages of this book are devoted to etiology, symptomatology and diagnosis of exophthalmic goiter, and the latter portion to the author's methods of treatment and presentation of statistics concerning the results. Except in very special cases the author's medical treatment is advocated. This in brief consists of elimination of foci of infection, psychotherapy, rest of body and mind, high caloric-low meat diet and the use of certain drugs. The author lists those he most commonly employs (and in order of importance) as: 1, quinin; 2, iodine; 3, eserine; 4, adrenal cortical substance; 5, the barbiturates; 6, ovarian substance; 7, insulin. The average duration

of active treatment was 8.4 months. There were no recurrences. There were but 12 deaths due directly or indirectly to exophthalmic goiter in a series of 3924 cases. No convincing evidence is presented of the value of quinin, eserin, adrenal cortex, ovarian substance or insulin. The author considers the determination of the basal metabolic rate and the Bram quinin test as the most useful diagnostic tests. There are numerous misleading or inaccurate statements such as "Ordinarily, the ingestion of 100 gm. of sugar causes no increase in the normal person's blood," (p. 237); "By its (the adrenal cortex) synergistic influence upon the pancreatic function it favors carbohydrate tolerance" (p. 333); "Diminished . . . calcium content is characteristic" (of the blood in exophthalmic goiter) (p. 116).

F. D.

SECURITY AGAINST SICKNESS. A Study of Health Insurance. By I. S. FALK. Pp. 423. Garden City, N. Y.: Doubleday, Doran & Co., 1936. Price, \$4.00.

THE medical profession is well aware of a steadily growing restlessness in regard to the economic aspects of medical service, and both the profession and the public are conscious of some fundamental weakness in the functional and economic relation between medicine and society. Much has been written on this subject, but nothing has been published previously which embodies such a comprehensive and accurate study of the problem, bearing on the American situation, as the book under review. It presents a study undertaken in search of a rational basis for constructive action on certain problems which arise out of illness and its social and economic sequelæ. The author's task has been to define these problems, and to seek out as objectively and vigorously as possible, the principles upon which constructive action should rest. This task has been carried out so well, that the book should do much to clear the smoky atmosphere in which so much confused discussion has taken place, and should create a new and well-defined point of departure for future exploration, a new map, it seems, which no one venturing into this controversial region of social reform can afford to ignore.

The first part of the book discusses the need for group payment of sickness costs in the United States. The costs of illness as an important cause of social and economic insecurity are examined, and this examination reveals that the greatest need is not more money for the purchase of medical care, but better ways of budgeting the costs and of spending the money wisely and effectively. This can be done by the group payment of sickness costs, distributing them among groups of people and over periods of time. Health insurance is the rational method of effecting this desirable distribution of the costs involved in sickness, which consist of the costs of medical care and the loss of wages through sickness. The author emphasizes that it is not the practice of medicine that is under discussion, but the methods of paying for medical care. How medicine should be practiced, and how it should be paid for, must be kept as far as possible, distinct.

The second part of the book consists of a study of European experience with health insurance; careful analyses of the German, British, French and Danish plans are discussed.

The third part is a discussion of the basis for an American program, beginning with certain conclusions to be drawn from foreign experience with health insurance. It is of interest that, outside of the United States, most progressive countries of the world have attempted to provide through insurance against the uncertain financial burdens of sickness.

In reviewing the experience of Europe, certain broad tendencies are observable, some of which are of special interest to the medical profession. Health insurance has moved steadily from voluntary to compulsory sys-

tems, and no country has gone back from a compulsory to a voluntary system. The breadth of coverage, starting with the more poorly paid workers, has tended to include people at somewhat higher economic levels. The types of medical service have also tended to extend to include more than the services of the family physician. Health insurance has contributed to the improvement of public health and to the development of prevention, as well as to the cure of illness. It is evident that the medical profession should coöperate more fully in the formulation of plans than was done in Europe, where lay control of professional matters has been a deep-seated source of irritation to the medical profession. The profession should have a strong and authoritative voice in consulting the representatives of the people who must eventually determine the system of health insurance that may be put into operation. Health insurance has not developed into "State Medicine" in Europe, but has supported private practice and has acted as a bulwark against the control of medical practice by the state. Both the public and the profession in the various European countries studied, are convinced of the value of health insurance and are interested in extending rather than limiting its scope. Much that has been written concerns controversies rather than principles. European experience indicates the desirability of separating insurance covering the costs of medical care, from that covering loss of earnings through sickness, and especially from the certification of illness as a means of obtaining cash benefits to cover wage losses.

The author reviews the experience in the United States with workmen's compensation insurance, and concludes that health insurance should be built not upon this existing form of compulsory insurance, but upon a foundation more adequately designed for the purpose. The arguments for voluntary or compulsory health insurance are reviewed and evaluated, and the author reaches the well grounded conclusion that the welfare of the public and of the profession requires that group payment of sickness costs should be designed on a compulsory insurance basis. He then lays down what he considers the basic principles for an American program, which constitute the last and most important chapter in the book. These principles begin with certain axiomatic truths with which all intelligent people, both lay and professional, should find no difficulty in agreeing. These include the statement that the provision of good medical care is essential to the nation's well-being, that the cost of medical care varies among groups of people and over periods of time, that those who render medical care should be adequately remunerated and that the quality of medical care should not be sacrificed to economy of service.

The question before any reader of the book is how many of the 19 principles laid down are to be considered essential and desirable for strengthening the functional and economic relations between medicine and society. These principles are submitted for further study and consideration after the needs of this country and the experience here and elsewhere have been examined, and it is the hope of the author that his studies will contribute to a further understanding of the economic problems which arise out of illness and of measures which may be designed to deal with them. There is no doubt that a careful reading of the book will fulfill this hope.

G. R.

AKTIVE ENTSPANNUNGSBEHANDLUNG. Ein Neues Therapeutisches Prinzip mit Berücksichtigung der Sprache und Atmung. By DR. MED. JOH. FAUST, Hannover. Pp. 112; 20 illustrations and 2 plates. Leipzig: Hippokrates-Verlag, G.M.B.H., 1936. Price: Paper, Rm. 5; Bound, Rm 6.20.

THE author points out that under conditions of nervous tension incident both to physical and mental stress there is an increased tonus of all skeletal

and probably much involuntary muscle; an increase of tonus that, if the cause be excessive, may continue for an increasing time after the exciting cause has ceased, and to increasingly higher levels. This increased tonus is in no small degree responsible for the various fatigue phenomena from which such patients suffer. The author claims that by directing the attention of the patient to the excessive tonus of his skeletal muscles and having the patient voluntarily relax these muscles frequently, there will result not only a great saving of energy and a relaxation of nervous tension but a return to normal in the overactive vegetative system as well. Particular attention is paid to the mechanisms of breathing and speaking. The material is well presented and the argument is convincing. R. K.

PSYCHIATRY FOR PRACTITIONERS. Volume 7 of The Oxford Medicine. By various authors. Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (Hon.), Hersey Professor of the Theory and Practice of Physics, Harvard University; Physician-in-Chief to the Peter Bent Brigham Hospital, Boston. Pp. 634, with 12 pages of Supplementary Index. New York: Oxford University Press, 1936. Price, \$10.00.

DISORDERS of the mind are among the commonest ills of man. They may arise from, or be conditioned by, all kinds of bodily ailments. They may give rise to symptoms that will often mislead the physician into a diagnosis of somatic disease. It is obvious, therefore, that every practitioner must be his own psychiatrist in dealing with the great majority of the mental problems of his patients. (Parenthetically, it might be said with almost equal justice that the psychiatrist needs to be a good internist.) This book is therefore a much needed and a very welcome one since it has been written by a group of eminent psychiatrists expressly to meet the needs of the practitioner of medicine. There are chapters on the recognition and the management of the beginning of mental disease, the psychiatry of childhood, postencephalitic and posttraumatic behavior disorders, mental deficiency, the psychopathic personalities, the toxic reaction psychoses, paranoia and paranoid conditions, the dementia præcox group, the manic-depressive type and involutional melancholia, and the psychoneuroses. The several sections are of a uniformly high standard of excellence; of particular interest to practitioners will be the chapters on the beginnings of mental disease and the psychoneuroses. With the possible exception of the chapter on the psychopathic personalities, there has been avoided the error of bogging down the general medical reader in too much technical psychiatric cant. Likewise the writers have taken a broad viewpoint of their subjects, save for an overemphasis on psychoanalysis in the chapter on the psychiatry of childhood. The book is warmly recommended, R. K.

DIE "ATYPISCHE" PNEUMONIE. Eine klinisch-röntgenologische und differential-diagnostische Studie, zugleich ein Beitrag zur Frage der "Grippe" und des Frühinfiltrats. (Special Vol. 6 der Sammlung Immunität, Allergie und Infektionskrankheiten.) By DR. MED. FRANK KELLNER, Facharzt für Lungenkrankheiten, leitender Arzt des Tuberkulosefürsorgestelle Kassel. Pp. 52; 10 illustrations. München: Otto Gmelin, 1936. Prices: Paper, M. 2.70; Bound, M. 3.60.

THE author concludes that (1) "atypical" pneumonia is not only a very variable but also a relatively frequent disease. The designation "atypical" is, therefore, misleading and ought to be discarded; (2) many cases of "grippe" are actually such "atypical" pneumonias; (3) a not inconsiderable number of cases which have been interpreted as the early infiltrative lesions

of tuberculosis are really such "atypical" pneumonia. These conclusions are fully justified on the basis of the author's extensive personal observations, in which close and frequent correlation between clinical and Roentgen ray findings was the important procedure, as well as on the basis of evidence from numerous sources in the literature. It might be added that many experienced clinicians have come to hold the same views. Nevertheless our textbooks on medicine have as yet taken almost no cognizance of these facts. The author's is a valuable contribution.

R. K.

TUMORS OF BONE. (Including the Jaws and Joints.) By CHARLES F. GESCHICKTER, M.D., and MURRAY M. COPELAND, M.D., Surgical Pathological Laboratory, Department of Surgery, Johns Hopkins Hospital and University, Baltimore. With Forewords by DEAN LEWIS, M.D., Professor of Surgery, Johns Hopkins Hospital and University, and the Late JOSEPH COLT BLOODGOOD, M.D., Former Clinical Professor of Surgery, Johns Hopkins Hospital and University, Baltimore. Pp. 832; 525 illustrations. Revised edition. New York: The American Journal of Cancer, 1936. Price, \$6.00.

THE need for a new edition of such a large book on such a specialized subject after the short span of 5 years is both a tribute to its original value and a confirmation of the wisdom of its publishers in distributing it at a relatively low price. Richly illustrated with excellent roentgenograms and histologic sections (both superior to those of the first edition), it provides much food for instruction and thought for students of this phase of neoplasia. With emphasis on the relation of normal bone formation to tumor development, a classification is offered based on: (1) Tumors related to osteogenesis (whether, *a*, derived from precartilaginous connective tissue or, *b*, related to growth subsequent to chondrification); and (2) tumors of non-osseous origin (such as Ewing's endothelial myeloma, multiple myeloma, fibrosarcoma, neurogenic sarcoma and metastatic carcinoma). The 25 chapters in the main follow this sequence, with forewords on clinical interpretations (Dean Lewis) and rules for diagnostic and therapeutic procedures (Bloodgood). The simplicity that is expressed as an aim in the preface would be distinctly furthered if stricter use of synonymous terms were observed in the chapter headings, classification (p. 2) and the text. For this revised edition, the section on non-osseous tumors has had to be rewritten and new chapters added on tumors of the cranial bones, jaws, and tendon sheaths, joints and bursæ. The supplementary chapters on bone diseases have also been enlarged (56 pages). It should be unnecessary to add that this book is an extremely valuable addition to the study of neoplasia, and a necessity for those dealing with bone tumors.

E. K.

FRIGIDITY IN WOMEN. Its Characteristics and Treatment. By DR. EDUARD HITSCHMANN and DR. EDMUND BERGLER, Director and Assistant Director, respectively, of the Psychoanalytic Clinic in Vienna. Authorized translation by POLLY LEEDS WEIL, of New York. Pp. 76. Washington: Nervous and Mental Disease Publishing Company, 1936. Price, \$2.00.

THIS monograph on Frigidity in Women by Hitschmann and Bergler has been sympathetically translated by P. L. Weil. The authors believe this widespread sex inversion is of a curable nature and may be overcome by a Freudian psychoanalysis. As a basis of study they portray the characteristics of female sexual life and its aberrancies. They have defined a concept of frigidity, discussed the symptoms and labelled the types of this inhibition.

Case records are introduced to bear out the contention that cures may be made through the methods of Freud. The enlightenment through sex education of the growing girl and young woman will, the authors believe, do much to prevent this type of neurosis in marriage. P. W.

A TEXT-BOOK OF PHYSIOLOGY. For Medical Students and Physicians. By WILLIAM H. HOWELL, PH.D., M.D., Sc.D., LL.D., Emeritus Professor of Physiology in The Johns Hopkins University, Baltimore. Pp. 1150; 308 illustrations. Thirteenth edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1936. Price, \$7.00.

As in previous editions of this work, a fairly good balance is maintained in including approved new material and withholding that which has not been sufficiently evaluated by specialists; in this way the size of the book has been but little increased in recent years. Admitting that it is impossible to satisfy everyone, the Reviewer feels, however, that more of the newer work should have been admitted, especially the newer work that modifies the statements that were added to recent editions. The steadiness of the demand for this premier American textbook on the subject is shown by the ability of the publishers to bring out a new edition biennially before the World War and triennially for the last seven editions.

E. K.

NEW BOOKS.

A Textbook of Medicine. By CHARLES PHILLIPS EMERSON, M.D., Research Professor of Medicine, Indiana University; Formerly Associate in Medicine and Medical Resident, Johns Hopkins University and Hospital, etc. Pp. 1296. Philadelphia: J. B. Lippincott Company, 1936. Price, \$8.00.

Greek Medicine. Volume XVIII of *Clio Medica*. By FRED B. LUND, M.D., Boston, Mass. Pp. 161; 7 illustrations. New York: Paul B. Hoeber, Inc., 1936. Price, \$2.00.

The Practice of Medicine. By JONATHAN CAMPBELL MEAKINS, M.D., LL.D., Professor of Medicine and Director of the Department of Medicine, McGill University; Physician-in-Chief, Royal Victoria Hospital, Montreal, etc. Pp. 1343; 505 illustrations (35 in color). St. Louis: The C. V. Mosby Company, 1936. Price, \$10.00.

The Life and Convictions of William Sydney Thayer, Physician. By EDITH GITTINGS REID. Pp. 243; illustrated. New York: Oxford University Press, 1936. Price, \$2.50.

Cosmetic Dermatology. With Dictionary of Ingredients; Discussion of Anatomic, Physiologic, and Pharmacologic Bases of Cosmetic Application; "Shelf-tested" Formulary; and Appendices on Odor and Color in Cosmetics. By HERMAN GOODMAN, B.S., M.D. Pp. 591. New York: McGraw-Hill Book Company, Inc., 1936. (No price given.)

Applied Dietetics. For Adults and Children in Health and Disease. By SANFORD BLUM, A.B., M.S., M.D., Head of Department of Pediatrics, and Director of Research Laboratory, San Francisco Polyclinic and Post-Graduate School. Pp. 408. Philadelphia: F. A. Davis Company, 1936. Price, \$4.75.

Applied Dietetics. The Planning and Teaching of Normal and Therapeutic Diets. By FRANCES STERN, Chief of Food Clinic, The Boston Dispensary; Assistant in Medicine, Tufts College Medical School, etc. Pp. 263; many tables and charts. Baltimore: The Williams & Wilkins Company, 1936. Price, \$3.50.

- Modern Treatment and Formulary.* By EDWARD A. MULLEN, P.D., M.D., F.A.C.S., Assistant Professor Pharmacology and Physiology, Philadelphia College of Pharmacy and Science; Lieutenant Commander, Medical Corps, U. S. Naval Reserve. Foreword by HORATIO C. WOOD, JR., Professor of Therapeutics in University of Pennsylvania, Graduate School of Medicine; Professor of Pharmacology and Physiology, Philadelphia College of Pharmacy and Science. Pp. 707. Philadelphia: F. A. Davis Company, 1936. Price, \$5.00.
- Diseases of the Coronary Arteries and Cardiac Pain.* Edited by ROBERT L. LEVY, M.D., Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University; Associate Visiting Physician and Cardiologist, Presbyterian Hospital, New York City. Advisory Editorial Committee: ALFRED E. COHN, JAMES B. HERRICK, CARL J. WIGGERS; 14 Contributors. Pp. 445; 97 illustrations. New York: The Macmillan Company, 1936. Price, \$6.00.
- Skin Diseases in Children.* By GEORGE M. MACKEE, M.D., Professor of Clinical Dermatology and Syphilology, New York Post-Graduate Medical School, Columbia University, and Anthony C. Cipallaro, M.D., Associate in Dermatology and Syphilology, New York Post-Graduate Medical School, Columbia University. Pp. 344; 153 illustrations. New York: Paul B. Hoeber, Inc., 1936. Price, \$5.50.
- Atlas of Human Anatomy.* With Explanatory Text. By JESSE FEIRING WILLIAMS, M.D., Columbia University. Colored Illustrations by Franz Forhse, University of Berlin, Max Brödel and Leon Schlossberg, Johns Hopkins University. Pp. 64. New York: Barnes and Noble, Inc., 1935. Price, \$2.00.
- The Physiology and Pharmacology of the Pituitary Body.* By H. B. VAN DYKE, Professor of Pharmacology, Peiping Union Medical College, Peiping, China. Pp. 577; 55 illustrations. Chicago: The University of Chicago Press, 1936. Price, \$4.50.
- International Clinics. Vol. IV. Forty-sixth Series,* 1936. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, Maryland, with 14 Collaborators. Pp. 351; many illustrations and 1 colored plate. Philadelphia: J. B. Lippincott Company, 1936.
- A Health Education Workbook.* For Teachers, Parents, Nurses and Social Workers. By KATHLEEN WILKINSON WOOTTEN, M.A., Professor of Health; Head, Department of Health and Physical Education, Georgia State College for Women, Milledgeville, Ga. Pp. 273. New York: A. S. Barnes & Co., Inc., 1936. Price, \$1.50 (Paper Binding).
- Cardiovascular Disease.* A New Aspect of Cause and Treatment. By JOSEPH H. SCHRUP, M.D., Dubuque, Iowa. Pp. 20. Privately published, 1936. Price, 12c.
- Bones.* A Study of the Development and Structure of the Vertebrate Skeleton. By P. D. F. MURRAY, M.A., D.Sc. Pp. 203; 45 illustrations. Cambridge: At the University Press; New York: The Macmillan Company, 1936. Price, \$2.50.
- Lectures on Embolism and Other Surgical Subjects (The Abraham Flexner Lecture, Series No. 4).* By GUNNAR NYSTROM, M.D., Professor of Surgery, University of Uppsala, Sweden; Chief of the Surgical Clinic and Director of the University Hospital, Uppsala. Pp. 213; 22 illustrations. Baltimore: The Williams & Wilkins Company, for Vanderbilt University, 1936. Price, \$3.00.

On the Incidence of Anæsthetic Complications and Their Relation to Basal Narcosis. By C. J. M. DAWKINS, M.A., M.D., B. Chir., D.A., Anæsthetist to the Dental Department, Middlesex Hospital; Anæsthetist to Hampstead General Hospital and to Paddington Green Children's Hospital, etc. Foreword by JOSEPH BLOMFIELD, P.B.E., M.D. Pp. 56. London: John Murray for the Middlesex Hospital Press, 1936. (No price given.)

"The prevailing use of basal narcosis has reached the point at which anæsthetists are well advised to take deliberate stock of the present results of practice, and to try and discern what disadvantages, if any, they are incurring to pay for the undoubted benefactions of preliminary sedation. Dr. Dawkins' thesis is a most valuable instrument towards this end." (From the Foreword.)

Volkserziehung im Dritten Reich. Mannesucht und Characterbildung. By HANS SUREN, Major a. D. Pp. 155. Stuttgart: Franckh'sche Verlagshandlung. Price, Rm. 2.80.

This book gives outlines for the education of German youth through disease and character building.

Elementary Pathology. An Introduction to the Process of Disease. By KEITH S. THOMPSON, Pathologist, Selly Oak Hospital, Birmingham; Formerly Lecturer in the Department of Pathology, University of Birmingham and Pathologist, Queen's Hospital, Birmingham. Pp. 74; 29 illustrations and 3 colored plates. Price, 10/6.

Medical Classics, Vol. 1, No. 1. (Ten Issues a Year). Compiled by EMERSON CROSBY KELLY, M.D., of the Department of Surgery, Albany Medical College. Pp. 78; illustrated. Baltimore: The Williams & Wilkins Company, 1936. Price, \$10.00 per volume.

NEW EDITIONS.

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The Principles of Bacteriology and Immunity. By W. W. C. TOPLEY, M.A., M.D., M.Sc., F.R.C.P., F.R.S., Professor of Bacteriology and Immunology, University of London; Director of the Division of Bacteriology and Immunology, London School of Hygiene and Tropical Medicine, and G. S. WILSON, M.D., F.R.C.P., D.P.H., Professor of Bacteriology and Applied Hygiene, University of London, London School of Hygiene and Tropical Medicine. Pp. 1645; 276 illustrations and 192 tables. Second Edition. Baltimore: William Wood & Co., 1936. Price, \$12.00.

Manual for the Medical Services of the Peiping Union Medical College Hospital. Edited by F. R. DIEUVAIDE, Head of the Department. Pp. 204; 3 plates. Fifth Edition, revised by the Staff of the Department of Medicine. Peiping: n.p., 1936. Price, \$1.50. For sale by the Stores Division, Peiping Union Medical College, Peiping, China.

"This Manual, as its title indicates, is intended primarily for the use of the staff of the Medical Services of the Peiping Union Medical College Hospital, especially for the resident staff, and for students. It embodies the practice of this institution in the examination and treatment of patients on the services administered by the Department of Medicine." (From the Editor's Preface.)

PROGRESS OF MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF
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THE HEMORRHAGIC TENDENCY OF OBSTRUCTIVE JAUNDICE.

ALTHOUGH Petit³⁵ published his discussions on biliary obstruction in 1743 and Bobbs³ performed the first cholecystotomy in 1868, it was not until 1891 that the first good description of the hemorrhagic tendency in obstructive jaundice was given, by Smith.⁴² The cause of the hemorrhage has never been understood even though many theories have been advanced in an attempt to explain it. Studies of the bleeding time and coagulation time of the blood in the jaundiced patient give no information as to whether bleeding will or will not occur after operation. Certain of the patients with ductal obstruction for variable periods exhibit no evidence of an increase in the clotting time of shed blood. Others have alterations of the clotting time so that shed blood does not coagulate in the normal period of time, as estimated by one method or another. There appears to be some change from the normal in clot retraction. However, patients with a prolonged clotting time are not necessarily the ones who bleed after operation. In a study of the hemorrhagic tendency in patients with bile-duct obstruction Bancroft, Kugelmass and Stanley-Brown² found that the coagulation and bleeding time were of very limited value in prognosticating postoperative hemorrhage.

It is well known that fatal hemorrhage in obstructive jaundice is rare prior to operation. There is, moreover, no absolute parallelism between the duration of the jaundice and the tendency to hemorrhage. In general, it is believed that the greater the liver injury the greater is the tendency to postoperative hemorrhage. It is for this reason that bleeding occurs more frequently in patients with obstructive jaundice from malignant lesions, especially when the malignancy also involves the liver.

The degree of bile-pigment retention in the blood is not always a criterion of a hemorrhagic tendency, but hemorrhage is more frequently observed in the severely jaundiced patients. We have recently observed fatal hemorrhage in a patient with a long standing biliary fistula and such cases have been reported by Linton^{27b} and Judd, Snell, and Hoerner²⁰.

There can be little doubt but that in general, surgeons are agreed that the more severe the liver injury the greater the tendency to post-operative bleeding. That long-standing obstruction and infection can cause a variety of degenerative hepatic lesions cannot be doubted. It is also generally agreed that hemorrhage is rare in hemolytic or catarrhal jaundice. In each of these conditions liver injury is rarely a prominent feature of the disease.

Calcium Many years ago Mayo-Robson³² suggested that the administration of calcium salts would be beneficial in restoring a disturbed calcium balance in the jaundiced patient. It was apparently his opinion that the bilirubin which was present in the serum in obstructive jaundice bound the calcium so that it was not available for the process of blood clotting. Because calcium is known to play a part in the coagulation of blood, its use became widespread even though, with one exception, no one has demonstrated a calcium deficiency in obstructive jaundice in the clinical patient as a routine finding.

Perhaps Mayo-Robson believed that the bile pigment which was eliminated in the urine of the patient with obstructive jaundice carried with it calcium from the serum. It may be stated that there are not now available any studies on calcium excretion in the urine of jaundiced patients.

Buchbinder and Kern⁴ have reported a progressive decrease in serum calcium in experimental jaundice. They used young puppies. They also reported 3 patients with jaundice who had low serum calcium values which returned to normal with a decrease of the jaundice. The data of these workers and of Kirk and King²⁴ and Carr and Foote⁸ stand alone in this respect in the wealth of data which has now been accumulated. King and Stewart²² suggested that the calcium combined with the bile pigment to render it less toxic, and King, Bigelow and Pearce²³ suggested that when the calcium combined with the bilirubin, less calcium was available for the clotting process.

Ravdin, Riegel and Morrison^{36a} found no appreciable reduction in the serum calcium of jaundiced patients and dogs. Snell, Greene and Rown-tree⁴⁴ reported similar findings, as did Halverson, Mohler and Bergeim,¹⁷ Koechig,²⁵ and Walters and Bowler⁴⁸.

Several papers have appeared which have attempted to differentiate the rôles of ionizable and non-ionizable calcium in the clotting process. Vines⁴⁶ came to the conclusion that ionized calcium is not necessary in the clotting process. The addition of oxalate, citrate or fluoride to normal blood in amounts chemically equivalent to the total calcium of the blood does not inhibit coagulation. Vines believed that the above anticoagulants all inhibited clotting primarily, by combining with a calcium-containing complex; the amount of anticoagulant required to neutralize the action of the complex was in each case in excess of the chemical equivalent of the calcium attached to it.

Stewart and Percival⁴⁵ studied the delay in coagulation of ox blood after mixing it with varying amounts of anticoagulants, citrate oxalate, fluoride, and so forth. They decided that ionizable calcium had nothing to do with coagulation; if anything, it lengthened the coagulation time. They, however, did believe that a complex protein-calcium compound, the identity of which they did not determine, played a definite part in the clotting process.

Gunther and Greenberg¹⁶ have very thoroughly reviewed the relationship of the serum calcium to jaundice and have concluded that there is no proof of a calcium deficiency in obstructive jaundice, nor any direct proof that the diffusible or non-diffusible calcium was in any manner deficient. Only in those instances where there existed a considerable change in the serum proteins was there any alteration in the serum calcium distribution from the normal. There can be no doubt but that a low serum protein is occasionally observed in the jaundiced patient but there are no data which lead one to expect that these are the patients that may bleed after operation. In our experience, there has been no correlation between low serum protein, a normal or reduced serum calcium and the hemorrhagic tendency.

The available information on the effect of hypo- and hypercalcemia on the coagulation time of man or dog shows no constant change from the normal. We have observed a normal coagulation time in a young girl with parathyroid tetany who had a serum calcium concentration of 5.2 mg. %, as well as in a patient with hyperparathyroidism who has serum calcium concentration of 15.4 mg. %.

Our data do not agree with the results obtained by Gordon and Cantarow¹⁵ and Cantarow, Dodek and Gordon⁷ who found that parathyroid extract given to normal and jaundiced patients caused a consistent reduction in the coagulation time.

Since Whipple⁴⁹ and Walters,⁴⁷ independently, suggested the use of calcium solutions in the pre-operative preparation of jaundiced patients, it has been customary to use a solution of calcium salts intravenously before operation, in the majority of clinics in this country. If calcium salts are of definite value in preventing hemorrhage in these patients the mechanism by which they may act is not as yet understood. In view of the evidence that a serious calcium deficiency never exists, their value is indeed doubtful.

It is highly likely that many of those who use calcium are influenced by the old suggestion of Wright^{50a} that calcium salts were useful in controlling internal hemorrhage and the hemorrhage of the hemophilic conditions for which they are no longer used. Undoubtedly the observation of Lee and Vincent²⁶ that the addition of calcium chloride to the blood of jaundiced patients *in vitro* shortened the coagulation time influenced many clinicians. Whatever may have been the factors which led to the popularity of calcium therapy in the pre-operative preparation of the jaundiced patient, the fact remains that for a number of years in the face of evidence to the contrary, we were lulled to a sense of false security.

Fibrinogen. It is supposed by some investigators that in the presence of obstructive jaundice there might exist a deficiency of available fibrinogen since obstruction of the common duct results in a variable degree of liver damage.

The important part which the liver plays in maintaining the blood fibrinogen level has been studied by Foster and Whipple,¹³ Howe,¹⁸ Mann and Bollman,³⁰ McMaster and Drury,²⁸ and others. Although there is agreement that the liver is the chief source of the blood fibrinogen, it is generally agreed that the degree of liver damage necessary to produce a fall in the fibrinogen level is considerably greater than that met in simple obstructive jaundice. Various conditions often associated with obstructive jaundice, anemia, infection and tissue damage, are in themselves often associated with an increase in the blood fibrinogen. Colbeck¹⁰ reported low values for fibrinogen in cases of obstructive jaundice.

Moss,³³ on the other hand, in a very interesting study investigated the fibrinogen in experimental obstructive jaundice and concluded that there existed no deficiency of fibrinogen in this condition. We are in complete agreement with his findings^{36b}.

Repeated studies of the blood fibrinogen in patients and dogs with obstructive jaundice have shown, as a rule, an increase rather than a decrease in the fibrinogen content. These studies have recently been repeated and confirmed by Eagle¹².

Sedimentation Rate. In 1930, Linton^{27a} reported that the sedimentation rate of the blood would offer information of prognostic importance; but the sedimentation rate may be profoundly altered by so many factors coincidentally associated with obstructive jaundice that it seemed hardly possible that this test would prove of value. Anemia, infection, tissue injury and dehydration are frequently present; and, although each of these may affect the sedimentation rate, it may play little or no part in preventing the blood from clotting normally. The subsequent studies of Clute and Veal⁹ and Carr and Foote⁸ show that this method is not reliable in determining the presence of an hemorrhagic tendency. The method has been used extensively and while changes in the sedimentation rate may be of some value they cannot be relied upon to indicate the presence of the hemorrhagic tendency. To place such reliance on the data so obtained as to neglect adequate pre-operative preparation is to court disaster.

Changes in Protein Metabolism. It would appear that the hemorrhagic tendency of the patient or animal suffering from an obstruction of the common bile duct is not due to deficiency of any known substance in the blood which normally takes part in the clotting mechanism. It has, however, been suggested by Carr and Foote⁸ that "taurine, cysteine and related products are the protein products which most probably back up in the blood and collect in sufficient concentration in the circulating plasma to cause changes in the clotting mechanism." Thus, these authors believe that the hemorrhagic tendency in obstructive jaundice is due to the addition of an inhibiting substance which affects the clotting process.

The chemical evidence adduced by Carr and Foote⁸ for the rôle of cysteine in the hemorrhagic tendency of obstructive jaundice is somewhat difficult to evaluate. The suggestion concerning the conversion of cysteine into dextrose is on quantitative grounds inadmissible, the amounts of dextrose which could possibly be derived from such a source being negligible. Furthermore, while sulphates are the normal products of cysteine and cysteine metabolism we are not aware of any evidence

that sulphites are end products. The statement that "sodium plumbite will convert cysteine to disulphids" is not in agreement with the facts known to us.

The evidence presented for the isolation of bromphenylmercapturic acid lacks definite proof. Moreover, there does not appear to be sufficient quantitative distinction between the amount of this compound produced by jaundiced dogs and that produced by normal dogs under the same experimental conditions. It is to be regretted that the figures showing an increase in the ethereal sulphates in the later stage of the disease, as mentioned by the authors, were not given.

It has been our experience that in patients with complete common duct obstruction hemorrhage prior to operation is of much rarer occurrence than postoperative hemorrhage. Rather have we observed that hemorrhage occurred at a time when bile was flowing freely from the common duct and the liver had had a chance again to resume, at least partially, its normal function.

It is a well-known fact that the administration of glucose profoundly affects the blood-guanidine concentrations observed after the liver necrosis caused by chloroform and carbon tetrachloride.

Should the mercaptans prove to be an important factor in the hemorrhage of obstructive jaundice, the rationale of glucose therapy is still further strengthened since Abderhalden and Wertheimer¹ found that animals receiving brombenzene excrete practically no bromphenylmercapturic acid when on a high-carbohydrate diet.

It is unfortunate that with so little factual evidence in favor of this theory it should have been so readily accepted. Much of the reasoning advanced by the authors was admittedly theoretical when applied to the data obtained from experiments. It is to be hoped that additional data will be published in order that we may determine whether the data fit the theory. It would have been best had the theory been built around the evidence.

Ivy or Venous Pressure Bleeding Time. Ivy, Shapiro and Melnick¹⁹ point out the unreliability of judging "bleeding tendency" in jaundice by a study of blood coagulation factors, such as changes in calcium, platelets, thrombin, fibrinogen, sedimentation rate, and by the use of the Kugelmass "clotting index." They have discussed the determination of blood coagulation time as an index of the bleeding tendency and state that from a study of medical literature the conclusion is that "the only condition in which a prolonged coagulation time is diagnostic is hemophilia." Nevertheless, they studied coagulation time in jaundiced patients by four different methods. All the cases studied except one had normal coagulation times.

Ivy and his associates¹⁹ believe that the only determination of value in deciding whether the patient will bleed, is a determination of actual bleeding time. The method which they have used is as follows: A cuff of a sphygmomanometer is applied around the arm, with a pressure of 40 mm. of mercury, enough to cut off effectively the venous return. The ordinary Duke puncture is made in the skin of the forearm near the elbow over the pronator muscles and the time at which bleeding stops is noted. The use of the cuffs, by increasing pressure in the capillaries and arterioles eliminates the factor of "capillary tonus" and gives a situation "comparable clinically when ether, shock, operative trauma.

etc., results in capillary paresis and bleeding." Normal bleeding time averaged about 180 seconds. "When the method was tried on a number of cases of jaundice, it was found that often, when the Duke's bleeding time was normal, the venous pressure bleeding time was definitely prolonged." These cases were frequently found to be ones which later bled either spontaneously or after operation.

The Effect of Viosterol in Jaundice. McNealy, Shapiro and Melnick²⁹ studied 810 unselected cases. These patients had common duct stones, cirrhosis of the liver with jaundice, toxic hepatitis, catarrhal jaundice, primary and metastatic carcinoma of the liver, or carcinoma of the bile ducts or head of the pancreas. Others had liver damage but no jaundice, cardiac decompensation, various types of blood dyscrasias, purpuras, anemias, or hemorrhage after tonsillectomy. The authors concluded that no single method of predicting the bleeding tendency is applicable to all types of hemorrhagic diatheses, but that in jaundice or any liver deficiency the only reliable criterion is a bleeding time of more than 240 seconds by the Ivy method. They believe that the mechanism of this is the fragility of the clot in hepatic insufficiency. The pressure of 40 mm. of Hg is sufficient to cause lack of fixation of the clot, or to detect a latent failure of small blood vessels to contract and retract normally.

They found viosterol of value in reducing the bleeding time in: (1) operation for cholecystectomy or choledochotomy; (2) exploration for malignancy; (3) medical cases of gall-bladder disease or common duct stone; (4) catarrhal jaundice; (5) cirrhosis of the liver, if the disease is not too far advanced.

They found viosterol of no value in: (1) medical cases of malignancy; (2) jaundice due to cardiac decompensation, pneumonia, toxic hepatitis, Banti's disease or portal thrombophlebitis; (3) blood dyscrasias, such as pernicious anemia, leukemia, secondary anemia, hemophilia, purpura, scurvy, and endocarditis.

The disturbances in vitamin utilization and storage in obstructive jaundice require further study.

Glucose. The simultaneous use of glucose and calcium in the pre-operative preparation of the jaundiced patient has resulted in a marked decrease in the incidence of postoperative hemorrhage. Since no deficiency exists in the serum calcium in the majority of patients with obstructive jaundice it seems highly possible that the beneficial effect of the pre-operative treatment may be ascribed to the use of glucose prior to operation.

As early as 1894, Wright^{50b} had observed a decrease in the coagulation time after the ingestion of a meal; 30 years later, Cannon and Gray⁶ showed that adrenalin, which mobilized the blood sugar, caused a reduction in the coagulation time. In 1929, Partos and Svec²⁴ reported a direct relationship between the blood sugar concentration and the coagulation time; but until our earlier studies^{56a} were published no data existed on the effect of glucose alone on the coagulation time of the jaundiced patient. In the studies prior to our report (Schreiber²¹, Kehr²¹, Walters⁴⁷, Whipple⁴⁹, and Mayo³¹), the use of glucose in the pre-operative preparation of jaundiced patients was invariably associated with the administration of calcium to prevent hemorrhage.

Our earlier observations on the effect of glucose on the coagulation

time have been confirmed and extended and we have found no reason to alter our conclusions that glucose alone, given intravenously or by mouth, favorably affects the coagulation time in both the normal and jaundiced dog and in patients with obstructive jaundice when the liver damage is not too great. Following glucose therapy the abnormal clot retraction so often observed in jaundiced patients approaches the normal in appearance.

Later studies by Cowan and Wright¹¹ confirmed in the main our findings. These investigators, however, believe that the effectiveness of the glucose is directly related to the rise in the serum calcium which they found to follow the glucose injection. This is not a consistent finding nor does it always parallel the rise in blood sugar or the decrease in the coagulation time. Furthermore, since the injection of calcium intravenously in larger amounts than that mobilized by an injection of glucose has little effect on the coagulation time, we are not at all sure that their statement that "the effectiveness of the increased calcium called forth by the glucose injection in reducing the coagulation time would indicate that this freshly released calcium was in a more readily available form for taking part in the clot formation than that already present in the blood, particularly in cases of jaundice." The data given by Cowan and Wright are too few for generalizations, but they are interesting in that they confirm our observations on the effect of glucose on the coagulation time. It is not possible from the available data adequately to explain the action of glucose on the clotting process.

The Use of Blood in Preventing and Controlling Hemorrhage. It is not known who first used transfusions in the postoperative bleeding of jaundiced patients. Since the history of the widespread use of blood covers less than two decades it is reasonably certain that this therapeutic procedure is of relatively recent date. A survey of the literature discloses very few references to the use of blood in the pre-operative preparation of these patients.

The beneficial effects of transfusion in the presence of a hemorrhagic tendency are well known. They must vary, depending upon the cause of the hemorrhagic diathesis. It was believed for a time that in the hemorrhage associated with operations on the jaundiced patient they were the result of the sodium citrate which was used as an anticoagulant. Indeed, for a time intramuscular injections of sodium citrate were used in the pre-operative preparation of the patient. It was then demonstrated that unmodified blood was just as, or even more, efficacious.

In 1930, and again in 1935, we^{36a,b} called attention to the value of blood in the pre-operative preparation and postoperative care of the jaundiced patient. It was stressed that the primary attention should be directed against the hemorrhagic tendency before bleeding occurred. More recently, Judd, Snell and Hoerner²⁰ have supported this view.

Judd and his coworkers²⁰ have called attention to the possibility of anoxemia being a factor in the condition which the jaundiced patient presents. Rich,³⁷ Rich and Resnick,³⁸ Campbell,⁵ and Rosin³⁹ have pointed out the changes in the liver cells after subjection to oxygen lack.

Snell⁴⁰ has reported on the anoxic type of anoxemia which is present in chronic liver disease of the advanced type. He believes that the degree

of oxygen unsaturation of the blood in general reflects the condition of the patient. Judd and his associates²⁰ suggest that in the anoxic type of anoxemia, oxygen therapy be used, while if the anoxemia is of the anemic type transfusion also is indicated.

The general specific effects of the transfusion of blood in these cases are at times difficult to dissociate. There may be a deficiency in the oxygenation of hemoglobin, in the oxygen carrier, or in the blood flow. The portal stasis which Rous and Larimore¹⁰ showed to exist in obstructive jaundice will still further add to an oxygen lack in the liver lobules. Recently Goldschmidt, Ravdin and Lucké¹⁴ have shown a marked reduction of the oxygen saturation of the portal and hepatic venous blood during anesthesia with volatile anesthetics without ductal obstruction. The reduction of available oxygen to the liver cells from a variety of causes undoubtedly still further damages the hepatic parenchyma. This is a new approach to an old problem which has baffled investigators and clinicians for a long time. It was only 16 years ago that it was said that the hepatic parenchyma needed little oxygen to survive and function.³¹ The beneficial effects of a plentiful supply of oxygen against the necrotizing effects of certain anesthetics were also noted.¹⁴

The exact method by which blood transfusion prevents hemorrhage in the jaundiced patient and controls it is not as yet understood. It is possible that some substance necessary in the normal clotting process, at present not known, may be supplied. It is possible that anoxemia may be a direct or indirect factor. This may be in its relation to the liver itself or in relation to the general circulatory and systemic effects of anoxemia. The trail would seem to be narrowing.

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OPHTHALMOLOGY

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THE EFFECT OF TRYPARSAMIDE ON THE OPTIC NERVE.

EVER since the introduction of trypanosomiasis and of central nervous system syphilis, attention has been called to the possibility of optic atrophy resulting from its use. Most observers have noted visual disturbances in a certain number of patients, usually during the course of the first 4 or 5 injections. Although in the majority of cases, the disturbances are transitory in character and are not accompanied by any actual objective loss of vision, a few patients develop a sudden or gradually progressive reduction in vision which is apt to be permanent. No definite agreement has been reached as to the exact nature and etiology of the lesion, especially since attempts to reproduce the lesion in experimental animals have been essentially unsuccessful. Three main questions have been raised: 1, does trypanosomiasis have a direct toxic action on the optic nerve; 2, is the optic atrophy essentially a result of the primary disease of the central nervous system and, if so, does the trypanosomiasis activate this disease in or cause its extension into the optic nerve, and 3, is the presence of optic atrophy a contraindication to the use of trypanosomiasis? This review is intended merely to present an unbiased summary of the attempts which have been made to answer these questions.

Frequently there has been raised the question of whether atoxyl and tryparsamide are more toxic to the optic nerve than are other forms of arsenicals used in the treatment of syphilis. Mayer and Smith¹² quote Dancy as saying that "all the ocular changes take place as frequently during the use of other arsenicals and the use of tryparsamide is not contraindicated in my opinion when we have fundus changes. And it is my opinion that changes in vision and fields are temporary. . . ." Clinical impressions on this point are varied. Attempts to demonstrate a direct toxic action of tryparsamide on the optic nerves of experimental animals have been rather unsuccessful. In 1919, Brown and Pearce² studied the toxic effect of tryparsamide in experimental animals. They did not report any pathologic changes in the eyes. Young and Loevenhart,²⁰ in the experimental administration of atoxyl, tryparsamide and other arsenicals of a similar composition, found ophthalmoscopically filling of the optic cups in rabbits, and histologically edema and congestion of the nerve heads and congestion of the retinal and choroidal vessels. They believe that arsenicals, such as atoxyl and tryparsamide, with an amino group, or a substituted amino group, in a para position to the arsenic, produce optic nerve lesions in the rabbit. Organic arsenicals with the amino group, or substituted amino group, in the ortho or meta position to the arsenic, do not produce nerve lesions. They were of the opinion that the drugs which produced the lesions they described in animals would produce amblyopia in the human, but they did not believe that the amblyopia observed following the clinical administration of tryparsamide is identical with the experimental optic injury produced by using large doses of the drug. They stated that they knew of only one case without neurosyphilis or trypanosomiasis in which amblyopia followed the administration of tryparsamide. However, Woods and Moore¹⁹ report 6 cases of visual disturbance following the administration of tryparsamide to patients with syphilis but without involvement of the central nervous system.

In 1934, Lazar⁷ studied the effect of tryparsamide on the eyes of rabbits. Having in mind the statement of Collins and Mayou that the toxic effect of arsenates is to be found in the ganglion-cell layer of the retina, he examined histologically the retinas of rabbits after a series of weekly injections of tryparsamide. He found no pathologic changes. In 1 rabbit, killed 10 days after an injection of 1.5 gm. of tryparsamide, the retinas showed no marked pathologic changes, but multiple small foci of perivascular hemorrhage were present in the chiasm and throughout the substance of the brain. The axis cylinders near such foci in the chiasm were swollen, distorted and broken up. An extensive hemorrhage was found in the outer sheaths of the optic nerve. In another rabbit, edema was present in the retina around the optic disk and round cell infiltration and degeneration were noted in the ganglion-cell layer. The nervous system in this case showed changes characteristic of an endemic type of encephalitis frequently found in laboratory animals. Lazar concluded that he could not say with any degree of certainty that these changes were caused by the drug. Lazar also examined histologically the eyes of a man who had lost his vision suddenly following tryparsamide $2\frac{1}{2}$ years before. The optic nerves were atrophic and showed marked increase of intraneural connective tissue and of the sur-

rounding pia-arachnoid. The optic tracts were atrophic and showed complete absence of myelin with a mild glial proliferation. Multiple organized foci of softening were present in the occipital cortex, apparently the residual of previous hemorrhage. Lazar thought the optic atrophy to be syphilitic, though the areas of softening might have resulted from the toxic action of the tryparsamide.

In 1935, van den Branden and Applemans¹⁸ studied the toxic effect of tryparsamide in rabbits with and without experimental trypanosomiasis. A single injection of tryparsamide was never found to produce optic atrophy. Repeated weekly doses seemed to be more toxic to the optic nerves. Tryparsamide apparently produced vascular changes in the retina. The changes were more frequent in animals with trypanosomiasis than in healthy animals. In their opinion, tryparsamide probably lights up an affection of the optic nerves which are made more susceptible by the trypanosome infection of the nervous system.

Clinically, the disturbances of vision resulting from the administration of tryparsamide to patients with trypanosomiasis are strikingly similar to those seen in connection with tryparsamide therapy of neurosyphilis. Louise Pearce¹⁵ reported that of 77 patients with trypanosomiasis treated with tryparsamide, 9 developed visual impairment. Six recovered completely; in 3 there was some permanent damage. In all except 2 of the 9 patients there was severe involvement of the nervous system. No visual disturbances occurred in the early stages of the disease, irrespective of the system of therapy. On the resumption of the administration of tryparsamide after a rest period, none of the cases with visual disturbances had a recurrence or increase of symptoms. Pearce concluded: "It seems not unlikely, therefore, that the individual pathologic condition of the optic structures in advanced cases is the principal predisposing factor in the occurrence of the untoward effect." On the other hand, Barlovatz¹ reported that, in a group of 1700 patients with trypanosomiasis treated with tryparsamide, there were 11 instances of blindness of rapid onset which remained essentially permanent. The loss of vision seemed to be due to the toxic action of the drug. Barlovatz mentioned that the preparation used was of considerable age and he questioned the possibility of a change in its composition.

The findings of van den Branden and Applemans agree essentially with those of Louise Pearce. They noted that visual disturbances occurred essentially only in patients with abnormal spinal fluids. Of 70 patients with trypanosomiasis and more than 50 lymphocytes per c.mm. of spinal fluid, 21 showed visual disturbances, while of 48 patients with less than 50 lymphocytes per c.mm. of spinal fluid, only 3 showed visual disturbances. The visual disturbances with tryparsamide come on less abruptly than with atoxyl, in their opinion, and are usually controlled by stopping the drug. With atoxyl, the loss of vision almost always progresses to complete blindness. They state that edema of the optic disks has been observed in untreated cases of trypanosomiasis, which fact lends support to the supposition that tryparsamide may simply light up a latent affection of the optic nerves.

From these reports, it seems apparent that the cases of visual dis-

turbance noted in the course of tryparsamide treatment of trypanosomiasis may be of two different types, a transitory or mildly progressive reduction of vision which may represent the activation of a preëxisting lesion in the nerves, and a rather abrupt serious loss of vision without much tendency to recovery which may represent a direct toxic action on the nerves in a patient with an idiosyncrasy to the drug. It seems to me that these same two types of involvement are observed in the treatment of neurosyphilis with tryparsamide. Possibly, insufficient attention has been paid to the differentiation and appropriate handling of these two varieties of optic nerve involvement, although this difference has been hinted at in the work of several authors.

In their first report on the therapeutic use of tryparsamide in neurosyphilis, Lorenz and his co-workers^{10,11} stated that, when tryparsamide is used in 5-gm. doses at weekly intervals, after 4 or 5 doses approximately 40% of the patients complained of dimness of vision. This visual disturbance was transient in all but 2 of approximately 100 cases. The 2 in which the loss of vision persisted were far-advanced paretics who had had abnormal eyegrounds before treatment. No eye symptoms developed in patients to whom 3-gm. doses were given. They stated that tryparsamide possesses the potentiality of injuring the optic tracts and advised that it should not be used in cases showing degenerative changes in the retina.

In the reports presented to the American Medical Association by various neurologists and syphilologists after their first year of clinical use of tryparsamide, the percentage of patients with permanent objective loss of vision varied from the less than 1% of Lorenz and his associates to the 5.5% of Moore and Robinson¹³ and the 13% (2 of 15 cases) reported in the Canadian Medical Journal by Crawford.⁵ Lorenz and his associates noted visual disturbances in 13 of 185 cases of neurosyphilis. In 12, however, the vision returned completely to normal when the drug was stopped. Ebaugh and Dickson⁶ reported that 1 of 52 cases developed optic atrophy following the first course of tryparsamide. Of the more than 100 patients treated by Solomon and Viets,¹⁷ 3 developed apparently permanent impairment of vision. Cady³ tabulated the visual disturbances in the various types of neurosyphilis. Thus he found that, in a group of paretics and taboparetics, 26% complained of visual disturbances and 7% had objective loss of vision. In a group of tabetics, 23% had subjective and 10% objective loss of vision. Of cases with cerebrospinal syphilis, 26% had subjective and 9% objective visual disturbances. Of 15 patients with optic nerve disturbances 7 became worse under treatment.

Of the more strictly ophthalmologic reports, that of Woods and Moore¹⁹ was the first to appear. They classified their cases into those with subjective complaints, such as dazzling, without ophthalmoscopic or visual field changes, and those with objective findings, usually changes in the visual fields and occasionally reduction in central vision. They noted visual disturbances in 17.8% of 241 patients who had received more than 3000 injections of tryparsamide. In 10.6% of the 241 patients, objective findings were present. The changes in the visual fields were, as a rule, confined to concentric contraction with no change in the physiologic blind spot and no scotomas. The constriction of the visual

fields usually progressed gradually but was sometimes more acute. Two patients developed almost complete blindness within 1 to 4 days. The vision returned practically to normal within 2 to 4 weeks. One patient went on to practically complete blindness with advanced primary atrophy of the optic nerves. Woods and Moore¹⁹ stated that, in 80% of the cases, the visual disturbance developed by the time the patient had received 5 doses of the tryparsamide. Patients who had not reacted unfavorably by that time rarely showed any difficulty after further injections. They could establish no relationship between the size of the dose and the unfavorable reaction in the optic nerves. The majority of the reactions occurred in patients with neurosyphilis, but 6 were seen in patients without involvement of the central nervous system. Of 95 patients without evidence of a preëxisting ocular lesion, 20 (21%) developed visual disturbances, while of 15 patients with definite preëxisting syphilitic lesions of the eyes, 12 of whom had optic nerve involvement, 4 (33%) developed visual disturbances. However, Woods and Moore felt that "preëxisting syphilitic disease of the optic nerve or retina is not necessarily a contraindication to the use of tryparsamide." They stated further: "The fact that visual disturbances may arise in patients with normal eyes and that they may fail to develop in patients with outspoken syphilitic eye disease points to direct toxic action of the drug on the retina or optic nerve as a factor in their causation." In support of their belief in the toxic effect of tryparsamide on the optic nerves in spite of the absence of central scotomata, Woods and Moore note that atoxyl and arsacetin can cause gradual visual failure and constriction of the visual fields with no scotomas and no special involvement of the papillomacular bundle. The fundi are normal at first. Primary optic atrophy becomes visible later. They state that Birch-Hirschfeld, Igersheimer, and Sattler and Key have demonstrated that the chief action of these drugs is on the peripheral portion of the third optic neuron.

In 1930, Casten⁴ reported a case of loss of vision which he considered to be due to the direct toxic action of tryparsamide on the optic nerve. A patient with neurosyphilis who had had previously normal vision, fields and fundi developed blurring of vision following the second dose of tryparsamide. Within 5 days, vision was reduced to light perception. Noting that Solomon had reported finding complete demyelination of the optic nerves in a patient who became totally blind after treatment with tryparsamide, and that Fordyce and Myers had found that 80% of 50 patients treated with tryparsamide showed arsenic in the spinal fluid, Casten employed "forced" drainage of the spinal fluid (140 cc. being removed at one time) in the hopes of removing the arsenic. After 4 such drainages, central vision had returned to 20/15 but there was some residual contraction of the peripheral fields of the palpebral fissure type.

Lazar did not think that Casten had presented definite proof of arsenical poisoning in his case or that the removal of arsenic by spinal fluid drainage was a factor in the recovery of vision. He stated that Cornwall, Bunker and Myers had demonstrated quantitatively that there was less arsenic in the spinal fluid after the use of tryparsamide than after any other form of arsenical therapy. However, Lazar noted

that of 32 patients under tryparsamide therapy, 5 showed permanent loss of vision. He said, "The definite loss of vision so soon after the injection of tryparsamide leaves no doubt in my mind of a definite toxic effect of the drug on the visual apparatus of certain patients. This may cause serious permanent damage to a previously normal visual apparatus. Optic atrophy or constricted fields are positive contraindications." He suggested that certain patients might be especially sensitive to its toxic effects. Two of his patients with loss of vision gave positive reactions to intradermal tests with a 1 to 100,000 dilution of tryparsamide, while others with no visual disturbance gave negative tests.

Discussing Lazar's paper, Davis mentioned Reese's opinion that the changes in the eyes during the course of treatment are not due to the direct toxic action of the drug but are essentially syphilitic though they may be accelerated by the liberation of spirochetal toxins or by the changes in the tissues resulting therefrom. Davis stated, however, that he had observed several cases in which a striking, sudden reduction in visual acuity with marked constriction of the visual fields occurred and remained permanently, and "that visual changes develop, mostly transient, but some of them permanent, after the use of tryparsamide cannot be denied."

Some of the ophthalmologic reporters on the results of tryparsamide therapy feel quite strongly that there is no evidence in support of a direct toxic effect of tryparsamide on the optic nerve. Lillie^{9b}, in 1924, was the first to emphasize this point of view. Of his 114 cases 13 had visual disturbances after treatment (11%). In 9, the disturbances were subjective only. Definite decrease in vision and in perimetric fields occurred in only 4 (3.5%); 17 of these patients had had no previous antisypilitic treatment. Visual changes were found before treatment in 50%. Ninety-seven had had previous antisypilitic treatment. Only 20% of these showed perimetric field changes (prior to the use of tryparsamide). Central scotomas were not found in any case. In Lillie's opinion, ocular changes occurred as often with arsphenamine therapy as with tryparsamide. Of 9 cases with primary visual and perimetric field defects treated with arsphenamine, 4 became progressively worse, 2 improved, and 3 showed no change. He concluded that the use of tryparsamide is not contraindicated by pathologic changes in the fundus and that tryparsamide was no more harmful to the eyes than any other form of arsenic.

In 1925, Roth¹⁶ reported his observations on 22 patients treated with tryparsamide. In 5 there was no change in the fields, in 12 the fields increased in size, and in 5 there was a decrease in the fields (23%). Of a group of untreated patients 72 (62%) showed a decrease in the fields in the same period of time. Roth stated that in some of the cases dehydration and elimination by sweats and salines seemed to control a commencing limitation of the fields.

In the same year, Neff¹⁴ reported on the tryparsamide treatment of 15 cases with syphilitic eye lesions. He found that only 4 showed decrease in the visual fields, while in 3 the visual acuity improved and in 4 the visual fields improved. One case of optic neuritis cleared up with residual enlargement of the blind spot. He stated, "The evidence of

luectic changes of the optic tract do not, in our opinion, constitute an absolute contraindication to tryparsamide. In some cases the therapeutic response in the optic tract has been better than that noted under arsphenamine or neoarsphenamine."

The same view is held by some neurologists and syphilologists. In 1926, Cady and Alvis³ reported on the treatment of 180 cases with tryparsamide. Of these patients 153 had normal eyes; 8 (5.2%) showed visual disturbances which were permanent in only 2 (1.3%); 27 showed signs of optic nerve disease; 10 (37%) of which became worse, 4 improved, and 13 remained the same. Thus, 62% of cases of optic atrophy were either arrested or improved by tryparsamide. They concluded that tryparsamide can be used by experienced persons with comparative safety on patients having normal optic tracts, that patients with optic involvement such as contracted fields or abnormal fundi are more liable to injury by treatment than normal patients but show favorable response to treatment if properly controlled, and that the presence of objective findings is a contraindication for further tryparsamide for at least one month, when it may usually be resumed.

In 1932, Lees⁸ reported on the treatment of 21 cases of optic atrophy with tryparsamide. Treatment was started with iodides for 10 to 14 days. This was followed by intramuscular injections of bismuth for 3 to 4 weeks. Then tryparsamide was started in subtherapeutic doses of 0.5 gm. to 1 gm., gradually increasing to a dosage of 2 gm. to 3 gm. by the fourth or fifth injection if there had been no untoward effects. In 4 patients, the treatment could not be continued because of severe subjective symptoms; in 2 patients there was rapid deterioration of vision, apparently due to toxic action of the drug; in 3 patients the progress of the atrophy was not affected; but in 12 patients the atrophy was apparently arrested for periods ranging from 6 months to 5½ years. This was considered an unusually high percentage of arrested atrophy under any form of therapy.

After the treatment of 500 cases of neurosyphilis with tryparsamide, Lees is satisfied that the visual complications following its use are of minor importance in patients with normal sight and can be reduced practically to zero by proper interpretation of visual symptoms and by checking the fields and visual acuity at intervals during the course of treatment. He states that he had to stop treatment because of permanent damage to the eyes in only 5 cases (1%). Tryparsamide rarely, if ever, causes any damage to the optic nerve, in his opinion, if only therapeutic doses are administered and if appropriate measures are taken to prevent a Herxheimer reaction during the first few injections. He thinks that it is important not to continue its administration for a period of more than 8 to 10 weeks without giving an interval of 1 month's rest. The amount administered during each course should not exceed 24 gm. in an average adult male.

In 1934, Mayer and Smith¹² reported favorably on the tryparsamide treatment of 87 cases. No objective visual changes were observed in 34 cases of asymptomatic neurosyphilis and in 4 cases of meningovascular syphilis. Of 20 cases of tabes and 14 cases of paresis, 1 in each group showed a temporary contraction of the visual fields with a subsequent return to normal. They treated also 15 cases of optic atrophy.

Only 3 of these showed progression of the visual changes; 2 returned later to their original state and in only 1 did the vision show permanent progressive impairment.

Also in 1934, Lillie^{9a} confirmed his previous impression of the effect of tryparsamide on the optic nerves. He reported a group of cases showing a palpebral, slitlike contraction of the visual fields which he believes is seen only in patients with syphilis of the central nervous system. Histologically, such cases show a perineuritis of the optic nerves with resulting diffuse degeneration most marked in the periphery and, slightly, around the blood-vessels in the substance of the nerve with secondary gliosis. Lillie states that this is the type of field defect characteristic of most cases of objective visual disturbance following the use of tryparsamide. Apparently, in his opinion, the tryparsamide activates a latent ocular syphilis rather than exerts any direct toxic effect on the optic nerves.

In summary, it is obvious that the incautious use of tryparsamide in the treatment of neurosyphilis may result, in a certain percentage of cases, in serious damage to the optic nerves. Whether the optic nerve injury is due to a direct toxic action of the drug or to an excitation or exacerbation of a syphilitic lesion of the nerve seems relatively unimportant from a practical standpoint. The manufacturers of tryparsamide state that its use is contraindicated in cases which show ophthalmoscopic or visual field evidence of optic nerve disease. Apparently, this dictum is not universally accepted. In experienced hands, it may perhaps be used safely even in certain cases of optic atrophy. But it should not be forgotten that visual disturbances may develop in cases with previously normal eyes. Careful ophthalmoscopic and perimetric field examinations should be made in all patients who complain of disturbances of vision during the course of treatment with tryparsamide. Prompt discontinuance of the drug on the appearance of the first signs of organic involvement of the optic nerve will in most cases prevent the development of progressive and permanent loss of vision.

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PHYSIOLOGY

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Cystine Excretion in Cystinuria. JAMES C. ANDREWS and PERRY D. MELVIN (Departments of Physiological Chemistry and Urology, University of Pennsylvania). In a case of cystinuria accompanied by calculus formation in the right kidney, the urine, drained from that kidney after nephrolithotomy by means of a tube brought through the incision, was compared in composition with the urine voided through the urinary bladder from the other kidney. This comparison was continued during the whole postoperative period (about 11 days) during which the incision was kept open. This drainage from the operated kidney varied in volume from about 50 to 1000 cc. per day. Although it had the composition of normal urine as regards all ordinary constituents it failed to show any evidence of cystine, either free or as a hydrolyzable complex, in spite of having been produced by that kidney which had formed the cystine stones. The urine from the other kidney, obtained through the urinary bladder, contained amounts of cystine usually found in the urine of such subjects (about 0.3 gm. per day).

The percentage oxidation of the sulphur was as low in the drainage as in the urine, thus implying the presence of considerable amounts of a non-sulphate and non-cystine sulphur compound in the former. This compound is not precipitated by cuprous salts as are mercaptides. These findings suggest the possibility that the failure to find free cystine in the drainage results from a conversion of the cystine into some other substance in which the sulphur is neither in the -S-S- nor -SH form rather than from any functional difference between the kidneys as regards cystine excretion.

After the incision had been closed, separate catheterization of the two ureters produced urine samples both of which contained comparable amounts of cystine. After 7 months, bilateral catheterization produced urine samples averaging a slightly higher cystine concentration in the urine from the operated kidney than from the other.

Trepopnea. CHARLES C. WOLFERTH and FRANCIS CLARK WOOD (Robinette Foundation, Medical Clinic, University of Pennsylvania). Certain patients with heart disease who can lie comfortably in one recumbent position cannot tolerate another because of dyspnea and precordial discomfort. Cardiac enlargement and impairment of function of the heart are usually present in these individuals. The position preferred and that which cannot be tolerated vary somewhat in different patients. On account of a possible relationship to orthopnea, the name "Trepopnea" is suggested for this phenomenon. Movement of the heart in the mediastinum as the patient moves, causing obstruction of

certain mediastinal vascular channels, may be responsible for the symptoms of trepopnea. This mechanism may help to explain orthopnea and paroxysmal nocturnal dyspnea in heart disease.

Effects of Baths at Different Temperatures on the Circulation. H. C. BAZETT, J. C. SCOTT, M. E. MAXFIELD, and M. D. BLITHE (Departments of Physiology, University of Pennsylvania, and Hahnemann Medical College of Philadelphia). Human subjects under basal conditions (deprived also of water) entered a neutral bath at 35°. After a preliminary period of some hours, the bath temperature was either raised or lowered, and observations were continued for 1 to 3 hours. Bath and rectal temperatures, oxygen consumption, $A-V$ oxygen differences, blood pressures (optical method) and pulse-wave velocities (heart to subclavian, subclavian to femoral, subclavian to brachial, and femoral to dorsalis pedis) were measured. Cardiac outputs were calculated and also the effective peripheral resistance as judged by the relation of mean pressure to the cardiac output per square meter per minute.

Moderate cold increased the blood pressure through an increase in the peripheral resistance with little change in cardiac output. Warmth caused initially a fall in blood pressure from a decrease in the peripheral resistance which overbalanced an increased cardiac output. However, in the later stages of exposure to heat the blood pressure levels again rose; this was due to an increased peripheral resistance, for cardiac outputs were then returning towards the basal level, and stroke volumes were much reduced. This change, presumably compensatory in nature, accompanied incipient circulatory failure from diminished venous return. At the same time the large arteries constricted, as evidenced by increased pulse-wave velocities, so that they presumably could act as blood reservoirs. Owing to such constriction, and loss of distensibility, pulse pressure increased even when the stroke volume was reduced.

Resistance to dehydration proved to be much greater in the summer than in the winter, so that summer experiments were characterized by fall in the $A-V$ difference, fall in diastolic pressure, and a stroke volume which decreased only in the last stages of the experiment, while in winter experiments the $A-V$ differences increased, diastolic pressure rose, and the decreases in stroke volume were not only extreme, but occurred throughout the experiment.

Nutritional Edema: Its Effect on the Gastric Emptying Time Before and After Gastric Operations. P. M. MECRAY, R. P. BARDEN, and I. S. RAVDIN (Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania, and the Department of Roentgenology Hospital of the University of Pennsylvania). Patients having peptic ulcer or gastric malignancy frequently suffer from nutritional deficits for some time prior to the time at which they come for operation. When the dehydration which they so frequently exhibit is overcome such patients have a hypoproteinemia, with or without edema. On a number of occasions we have had evidence that a reduction of the plasma proteins may cause such changes in the gastro-intestinal tract after gastric operations as to mimic in every way a technical defect of the

anastomosis. We have studied the effect of a hypoproteinemia in dogs on the gastric emptying time before and after various gastric short-circuiting operations. The hypoproteinemia was induced by diet and plasmapheresis. As the total serum proteins were reduced the gastric emptying time increased. This was true for the intact gastro-intestinal tract and after various gastric operations. The delay in gastric emptying is, we believe, due to edema of the gastric wall. The stomach wall becomes edematous in the presence of marked hypoproteinemia. Gastric peristalsis is visible fluoroscopically after a barium meal but only small amounts of barium leave the stomach. The dogs with low total serum proteins which have been operated on showed a very marked delay in wound healing and considerable tendency to evisceration. With a return of the serum proteins to normal, gastric emptying time is reduced and wound healing progresses more normally.

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ORIGINAL ARTICLES.

THE PASSAGE OF FLUID THROUGH THE CAPILLARY WALL.*

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IN 1628, William Harvey, by describing the circulation of the blood, initiated a series of investigations which, beginning with the heart and larger vessels, have gradually penetrated further and further into the mysteries of the capillary network. Harvey's observations, though necessarily limited to the grossly visible portions of the circulatory system, led him to conclude that blood must pass from the peripheral arteries to the minute veins presumably through "porosities of the tissues." Approximately 50 years elapsed before the capillaries themselves were observed under the microscope by Malpighi and Leeuwenhoek. It seems as though investigation of the capillary circulation has never been able quite to overcome this initial handicap of half a century.

The occurrence of edema, an outstanding clinical problem even before the time of Galen, stimulated earlier physiologists and physicians to speculate concerning the mechanism which controls the migration of fluid through the capillary wall as well as its transportation and distribution throughout the body. In the normal individual the volume of tissue fluid suffers only transitory and relatively small changes, despite wide variations in water intake, exercise and posture. In patients with some tendency toward edema formation, on the contrary, the copious ingestion of water, or mere dependency of an extremity, may add to the normally meager amount of tissue fluid until clinical edema appears. These patients suffer apparently from a more or less serious breakdown of the normal mechanism of fluid transport.

* A lecture delivered before the Harvey Society, New York, November 19, 1936.
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The first reasonably complete hypothesis explaining how equilibrium between blood and tissue fluid might be maintained under diverse conditions was advanced by Starling,²¹ in 1896, and was later expanded to explain tentatively the pathogenesis of edema. Starling called attention to the fact that crystalloidal substances, such as salts, urea, creatinine and glucose, pass easily through the capillary wall and are present in approximately equal concentrations in blood plasma and tissue fluid. Such substances cannot exert a permanent osmotic pressure across the capillary wall and should not, therefore, affect the distribution of fluid except very temporarily. The plasma proteins, however, by reason of their greater molecular dimensions, are retained more or less efficiently by the capillary wall and can develop an osmotic pressure, amounting in man to approximately 26 mm. of mercury or 36 cm. of water. This colloid osmotic pressure of the blood tends to absorb fluid from the tissue spaces, while capillary pressure, on the contrary, tends to filter fluid from the blood stream into the tissue spaces. Thus the relative constancy of blood volume and tissue fluid volume should depend primarily upon the balance between these two forces. This ingenious concept, though theoretically sound, was for many years subject to criticism owing chiefly to the difficulty of measuring capillary blood pressure.

In 1917, Epstein⁷ emphasized the rôle of hypoproteinemia in the development of nephrotic edema. According to Starling's view, this type of edema could be explained logically by the low colloid osmotic pressure which, in association with a normal capillary blood pressure, would favor filtration of fluid and, at the same time, hinder absorption from the tissue spaces.

War edema, associated with protein starvation, was also found during this same period to be accompanied by hypoproteinemia, the edema disappearing when the plasma protein percentage rose to normal. Further clinical study by Krogh,⁹ Schade,²⁰ Govaerts,⁸ Meyer¹⁷ and others verified the importance of hypoproteinemia in some types of edema, but showed also that in other types the plasma protein percentage was usually within normal limits. The general problem of normal fluid balance and the clinical problem of edema then seemed too complex to be explained even partially by simple physical principles.

Until about 1917 the capillaries were generally thought to be inert, thin-walled tubes which conveyed blood through the tissues in whatever quantity the arteries and arterioles might supply. The extensive studies of Krogh⁹ and Lewis¹⁴ showed, however, that the capillary vessels are independently contractile and that they are capable of responding individually in a very delicate manner to the circulatory needs of the immediately adjacent tissues. But even so, the blood is still separated from the tissues it serves by a single layer of endothelial cells forming the capillary wall. Obvi-

ously interchange of substances between blood and tissues must depend fundamentally upon the properties of this membrane in association with the physical forces controlling the flow of blood past the membrane.

Important factors controlling the movement of fluids through a membrane are: (1) The total area of filtering surface available; (2) the properties, particularly the permeability, of the membrane itself, and (3) the pressures exerted on the fluids inside and outside the membrane.

The collective area of capillary wall available for fluid interchange is relatively enormous. Krogh⁹ estimated that the total surface of capillary wall in the body of an average-sized man must exceed 6300 square meters or 68,000 square feet. In other words, the collective area of vascular endothelium in the adult human body can be visualized as a microscopically thin membrane 3 feet wide and over 4 miles long. Obviously, very rapid interchanges are favored by areas of this magnitude.

In the second place, rapid interchange of water is aided by the inherent properties of the capillary endothelium which is far more permeable than other cellular membranes so far studied quantitatively. Under comparable conditions, water passes through the frog's capillary wall approximately 3000 times more rapidly than through the surface membrane of a typical cell and over 100 times more rapidly than through the membrane of the erythrocyte.¹¹

The significance of this extensive filtering area combined with great permeability can be expressed by a calculation which is admittedly approximate but illustrates the general magnitude of possible effects. Assuming that the capillary wall of man is as permeable as the frog's capillary wall, the total plasma volume of a man could be filtered through his calculated 68,000 square feet of endothelium within 10 seconds at a capillary pressure of only 10 mm. Hg if there were no force retaining fluids within the blood capillaries. Normally, the activity of the vasomotor system prevents the entire peripheral vascular bed from opening simultaneously. In addition, the plasma proteins, by their colloid osmotic pressure, limit the loss of fluid from the blood stream. Only in widespread injury of the vascular endothelium would it be possible for fluid to leave the blood at such a deleteriously rapid rate.

Quantitative studies of the third factor, namely, capillary blood pressure, offer some technical difficulty. Capillary pressure has been measured by many indirect methods, but the estimates thus obtained by different observers range from far below to far above colloid osmotic pressure. The relation between capillary pressure and fluid movement has been studied also by means of a plethysmograph which encloses a mass of tissue containing large numbers of capillaries. Results are often difficult to interpret because of changing diameter, pressure and rate of flow in the separate vessels

composing the capillary network. These variables can be reduced in number and more adequately controlled by studying single capillaries directly—thus limiting observation to what is, in fact, the smallest unit of the circulatory system.

To measure venous blood pressure directly it is necessary to use a needle small enough to be inserted easily into a vein; similarly, to measure capillary blood pressure directly the puncturing needle must be thinner than a single capillary. Chambers² had devised delicately adjustable micromanipulators for dissecting single cells. By means of this technique a micropipette can be introduced into the lumen of a capillary with the aid of a microscopic glass rod.^{11a} The minute orifice of the micropipette communicates through a continuous column of sodium citrate solution with a manometer and also with a simple device for altering rapidly the pressure exerted upon the fluid in the pipette. The capillary and pipette are observed under the microscope while adjustment balances the pressure in the apparatus against that in the cannulated vessel. When this equilibrium is reached the manometer indicates the level of capillary pressure. With slight modifications similar measurements can be made in arteries, arterioles, venules and veins as well.

From a large number of single determinations in the main anatomical subdivisions of the vascular tree, it became evident that average blood pressure declines very little in the arteries, but falls steeply as the blood enters the arterioles. This gradient does not stop with the arterioles but continues through the capillary network so that average blood pressure is considerably higher in the arteriolar portion of the capillary network than in the venous portion. Such a gradient of capillary blood pressure was observed in the four species studied (frog,^{11a} rat,^{11f} guinea pig^{11f} and man^{11c}), but the absolute level of pressure at which this gradient is maintained differs considerably according to species.

In the mesentery of the frog, for instance, the average blood pressure in those capillaries which are connected more directly with the arterioles is 14 cm. of water while in the venous capillaries, those emptying into the minute venules, average blood pressure is 10 cm. of water. In man, arteriolar capillary pressure averages 45 cm. of water, venous capillary pressure 22 cm. of water. According to Starling's hypothesis the colloid osmotic pressure of human and amphibian plasma should show corresponding differences. In general, this is the case since frog plasma has a colloid osmotic pressure between 7.5 and 13 cm. of water while the higher capillary pressure of man is balanced by a higher colloid osmotic pressure—approximately 36 cm. of water or 26 mm. of mercury. The rat and guinea pig with intermediate capillary pressures have also an intermediate colloid osmotic pressure. These findings are in accord therefore with the general concept that filtration, which is favored by excess of capillary pressure in the arteriolar part of the capillary

network, will be balanced by absorption through excess of colloid osmotic pressure in the venous part of the capillary network.

The gradients of blood pressure just described represent averages including large numbers of single determinations. Capillary pressure is really an extremely variable quantity. It changes spontaneously in the same capillary from moment to moment, and may differ widely in adjacent capillaries even though they arise from the same arteriole.^{11a} In the web of the frog, cutaneous trauma, such as that produced by a minute crystal of silver nitrate, leads to reflex vasodilatation and increased blood flow.^{11b} Capillary blood pressure rises conspicuously during hyperemia (*e. g.*, from 14 cm. of water to 23 cm. of water) and returns toward the lower resting level as hyperemia recedes.

If a micropipette be introduced into the venous limb of a capillary at the base of the human finger nail, pressure is usually found to be about 10 to 12 mm. of mercury, with barely measurable pulse pressure. If the skin be warmed locally to 43° C., capillary blood pressure often rises to well over 40 mm. of mercury.^{11c} Blood flow is rapid and pulse pressure is exaggerated temporarily during the period of hyperemia. On the contrary, cooling the skin at the base of the nail produces vasoconstriction and a distinct drop in capillary blood pressure which is followed, however, after a few minutes by a secondary rise associated with the reactive hyperemia which has been studied so thoroughly by Lewis¹⁴ and his co-workers.

Raynaud's disease is a vasospastic condition in which a period of arterial constriction is followed by reactive hyperemia and wide dilatation of arteries and capillaries in the affected digit. During the period of vascular spasm capillary pressure is extremely low, usually less than 8 mm. of mercury.^{11d} During recovery and its associated hyperemia, however, capillary pressure may for a brief period exceed 40 mm. of mercury, returning to normal as arterial tone once more increases.

Moreover, in man the position of an extremity modifies capillary blood pressure profoundly, owing in large part to the hydrostatic effect of the column of venous blood. In one study^{11e} pressure was measured in the arteriolar and the venous limbs of capillaries at the base of the finger nail while the hand was supported in various positions relative to the suprasternal notch. When the finger is above the suprasternal notch, capillary pressure, even in the arteriolar limb, is frequently less than the colloid osmotic pressure of the plasma proteins, that is, less than 26 mm. of mercury. As the finger is lowered beneath the suprasternal notch, both venous and arteriolar capillary pressure rise until finally even venous capillary pressure exceeds the colloid osmotic pressure of the blood.

These observations are mentioned to emphasize the extreme variability of capillary pressure which, under certain conditions, can be well above, or well below, the colloid osmotic pressure throughout

the entire capillary network. If the extremity is elevated or moderately cool, capillary pressure can be reduced to such an extent that filtration is impossible and absorption is favored even in arteriolar capillaries. Trauma, local heat or dependency, on the contrary, elevate capillary pressure so that filtration is favored and absorption is diminished or abolished owing to excessively high pressure even in the venous portions of the capillary bed.

Further development of microinjection methods made it possible to measure the filtration and absorption of microscopically small volumes of fluid by single capillaries of the frog's mesentery. If the flow of blood through a capillary be stopped suddenly by gentle compression with a glass rod, the corpuscles are at first distributed uniformly throughout the occluded capillary.^{11c} If capillary pressure is approximately 11 cm. of water, the corpuscles retain this distribution indefinitely. However, if capillary pressure is higher, the corpuscles move toward the obstructing rod rapidly at first, then more slowly as fluid is filtered from the trapped blood. On the other hand, if pressure is extremely low, absorption of fluid from the tissue spaces separates the corpuscles slowly and they gradually move away from the obstruction. Knowing the initial rate of this corpuscular movement, the diameter of the capillary and the area of endothelium involved, the rate of filtration or of absorption can be computed in terms of cubic micra of fluid per square micron of capillary wall per second. The effect of capillary pressure on fluid movement can then be shown by charting the rate of filtration or absorption against the observed blood pressure.^{11c} At capillary pressures in the vicinity of 11 cm. of water there is, in the frog's mesentery, little or no fluid movement in either direction. Capillary pressures above this level produce increasingly rapid filtration while lower pressures permit increasingly rapid absorption. It seems logical to regard 11 cm. of water as the effective osmotic pressure of frog plasma measured against its natural membrane, because at this pressure no fluid movement can be detected. The straight line relationship between fluid movement and capillary pressure is in accord with physical principles and provides evidence that the capillary wall acts as a passive (*i. e.*, non-secreting) membrane. The degree to which the rate of filtration is increased by unit rise in capillary pressure indicates that the capillary wall allows fluid to pass inward and outward with extraordinary facility. These semiquantitative observations led to the statement made previously that the frog's capillary wall is 3000 times more permeable to water than is the membrane of a typical cell.

If fluid movement in man is governed by the balance between capillary pressure and the colloid osmotic pressure of the blood, two things must follow. In the first place, as mentioned by Krogh,⁹ a relatively small elevation of venous pressure must cause fluid to accumulate in the tissue spaces so that the erect human being

is constantly near to edema. In the second place, with any given capillary pressure, a decrease in the colloid osmotic pressure of the blood should be accompanied by increased filtration.

In the normal human subject, the amount of tissue fluid is extremely small, and the capillaries are not suitable for direct measurement of fluid movement. Determining the rate of filtration, therefore, requires that a plethysmograph be used. The ordinary plethysmograph registers not only changes in the volume of tissue fluid but also those rapid fluctuations of volume which are due to dilatation or constriction of the arterioles, capillaries and venules. The amount of fluid filtered by slightly elevated venous pressures is relatively small and such minor accumulations, when measured by the ordinary plethysmograph, may be either hidden or grossly exaggerated by simultaneous changes in vasomotor tone. In order to avoid this source of error a special plethysmograph was constructed^{10,12} to measure at intervals the volume of a segment of forearm under an external pressure of 200 mm. of mercury. This pressure collapsed the venules, capillaries and arteries during each estimation and vasomotor changes did not then interfere with the measurement of the volume of extravascular fluid.

When a pneumatic cuff of sufficient width is wrapped around the upper arm and then inflated, capillary pressure rises rapidly until it equals or slightly exceeds the pressure in the armlet.¹⁵ The relation between the rate of filtration and capillary pressure has been studied in man, therefore, by measuring tissue volume repeatedly before, during and after graded venous congestion.^{10,12} Other things remaining constant, the higher the venous pressure, the more rapid is filtration as measured by increase in the volume of the congested forearm. At the end of the period of congestion, deflating the cuff allows venous pressure to fall to normal and forearm volume returns to the control level as the fluid previously filtered is reabsorbed by the capillaries or conveyed from the tissues by lymphatics.^{10,12}

Knowing the volume of the forearm within the plethysmograph and the total volume of fluid filtered over a given period, the rate of filtration can be calculated in terms of cubic centimeters of fluid passing per minute into 100 cc. of forearm tissue. When the observed rates of fluid movement are charted against venous pressure it appears that the rate of filtration is directly proportional to the venous pressure.^{10,12} Filtration and the accumulation of tissue fluid can be detected by the plethysmograph at venous pressures as low as 15 to 20 cm. of water. In that sense man is always very close to edema but, fortunately, other factors prevent outspoken edema from developing.

At this point it seemed advisable to determine to what extent this filtration concentrates the blood as it passes through the congested capillary bed of the forearm. After the subject had been

recumbent for a suitable period, venous pressure in one forearm was raised to 20, 40, 60 or 80 mm. of mercury while the other forearm served as a control.¹³ Unilateral venous congestion was continued for 30 minutes and then samples of venous blood were removed simultaneously from both arms. The heparinized blood was used to determine the erythrocyte count, cell volume, hemoglobin and plasma protein. Appropriate calculations showed that with a venous pressure of 20 mm. of mercury the amount of fluid lost by 100 cc. of blood is relatively small, not over 3 cc. The volume of fluid filtered becomes greater with each increase of venous pressure. When the congesting pressure reaches 80 mm. of mercury as much as 20 cc. of fluid may be filtered from 100 cc. of blood, representing a loss of approximately one-third of the plasma volume.

Even though slight elevation of venous pressure produces considerable filtration, dependent edema does not appear in the erect human subject. Fortunately the tissues resist, at least temporarily, the distention produced by the accumulation of abnormal amounts of extravascular fluid. When venous pressure is elevated, filtration as measured by the plethysmograph is most rapid during the first 5 minutes but then becomes slower and may even cease entirely though congestion continues. For example,¹² a venous pressure of 60 cm. of water at first filters fluid at the rate of 0.16 cc. per 100 cc. of tissue per minute and, if this initial rate were to continue, would produce pitting edema in 1 hour. However, repeated measurement reveals that at the end of 1 hour fluid is accumulating in the tissue spaces at only one-quarter the rate observed during the first 5 minutes. The appearance of edema is correspondingly postponed. At lower venous pressures, for instance 20 cm. of water, filtration may cease altogether even though venous congestion continues.

Apparently extravascular fluid distends the tissue spaces by developing a tissue pressure which at the same time diminishes progressively the effectiveness of a given capillary pressure in producing further filtration. The physiologic importance of this tissue pressure is probably considerable. Turner, Newton and Haynes²³ have shown that quiet standing places a distinct burden on the cardiovascular system, even to the point of producing dizziness and fainting in a certain number of subjects. Under ordinary conditions a fairly large proportion of the human body is below heart level. Hydrostatic pressure in the veins favors the filtration of fluid from the blood into these dependent tissues. The development of tissue pressure not only prevents the accumulation of edema fluid but also guards against the dangerous loss of fluid from the blood stream, the volume of which must be kept above a certain minimal level if circulatory function is to continue. However, the mere fact that edema does develop eventually indicates

that this protective mechanism is effective only temporarily and that it fails under long-continued stress.

The filtration produced in the human forearm by a given venous pressure depends also on temperature.¹² Warming the forearm from 14° to 44° C. approximately doubles the rate of filtration observed with a venous pressure of 60 cm. of water. This increased filtration is probably due to opening of capillaries which are closed at the lower temperature and possibly to increased capillary pressure secondary to the vasodilatation which heat produces. Drury and Jones⁶ had found earlier that high temperatures increase the filtration of fluid in the leg when measured by changes in total limb volume recorded with the usual form of plethysmograph.

It was mentioned previously that if Starling's hypothesis is applicable to man, lowering the colloid osmotic pressure of the blood should increase the rate of filtration produced by any given capillary pressure. The association of hypoproteinemia with the nephrotic and nutritional types of edema offers presumptive evidence in this direction but additional observations on normal human subjects seemed desirable. Thompson, Thompson and Dailey²² showed that when the human subject stands quietly, blood volume is diminished by as much as 400 cc. as fluid filters from the blood into the tissues of the legs. This fluid contains relatively little protein so that the protein percentage of the circulating blood rises while the subject stands quietly. The physical effects of changing colloid osmotic pressure can be measured by comparing filtration rates in the forearm produced by a given venous pressure while the subject stands and then while he reclines. In each of 6 experiments standing elevated the colloid osmotic pressure of the blood and at the same time diminished proportionately the rate of filtration produced by a given venous pressure.¹⁰ Lowering the colloid osmotic pressure by 1 cm. of water increases the rate of filtration by approximately the same amount as does raising the venous pressure by 1 cm. of water. The effects of these two forces on filtration are similar in quantity but opposite in sign, as would be expected from principles.

The preceding discussion has summarized physiologic evidence that the normal capillary wall exhibits the properties of an inert (*i. e.*, non-secreting) membrane and suggests indirectly from several angles that the capillary wall is relatively impermeable to protein. Chemical studies by Loeb¹⁶ and others compared the concentrations of electrolytes in edema fluid and blood serum without detecting any chemical evidence that the capillary wall behaves differently from collodion membranes which are permeable to water and electrolytes, but impermeable to protein. Though the electrolyte concentrations in blood serum and edema fluid are not quite identical, these slight differences persist even though the two fluids are separated by collodion membranes instead of the capillary wall.

In general, these differences follow qualitatively the requirements of the Gibbs-Donnan principle and can be ascribed to the known physical forces affecting equilibria across semipermeable membranes.

Drinker⁵ and his co-workers have called attention to the high concentration of protein often found in mammalian lymph. The protein content of lymph, which is formed slowly during rest, may be as much as 4.5%. Mild venous congestion prevents reabsorption of fluid and increases the flow of lymph. Under these conditions, the protein in lymph approaches 0.5% and is occasionally even less. This protein must originally come from the capillary filtrate and indicates that small amounts of protein can pass through the capillary wall. Apparently filtered fluid is easily reabsorbed while protein, once outside the capillary, does not return to the circulating blood so easily. The studies of Clark³ have shown that in the rabbit's ear capillaries grow into an area, function actively for a time, then disappear to be replaced by others. This renewal of units is logical enough when wear and tear is taken into account. It is still entirely a matter of conjecture as to whether protein passes through the walls of immature and senescent capillaries in greater amount than through the walls of fully mature units. Of greater physiologic significance are the questions, "To what extent on the average does the capillary wall retain protein?" and "Is the colloid osmotic pressure of the blood, as measured *in vitro*, very much greater than the effective colloid osmotic pressure of the blood *in vivo* against its normal membrane, the capillary wall?"

The effects of high venous pressure on the blood passing through the congested forearm were mentioned previously with reference to the volume of capillary filtrate. These same observations,¹³ involving unilateral venous congestion, were used to estimate the amount of protein in this capillary filtrate. At a venous pressure of 40 mm. of mercury, no loss of protein could be detected in the normal human subject, but the amount of capillary filtrate at this pressure is so small that the result may well be discounted. At 60 mm. of mercury, the capillary filtrate was greater in volume and contained on the average 0.3% protein or 4% of the total plasma protein, indicating that under these conditions the capillaries of the human forearm are 96% efficient in retaining protein.

Normally the amount of tissue fluid is extremely limited and it has not thus far been possible to obtain samples of capillary filtrate or tissue fluid for analysis. Edema fluid offers the nearest approach to tissue fluid, but interpretation of results is uncertain since inflammatory or degenerative changes as well as reabsorption, if present, would tend to elevate the protein content of edema fluid above that of normal capillary filtrate. The mechanically produced edema fluids probably approach the original capillary filtrate in their protein content, or at least indicate roughly to what extent the capillary wall can retain protein even under abnormal conditions.

Subcutaneous edema fluid from patients with nephrosis usually contains from 0.02 to 0.2% protein. Subcutaneous edema fluid of non-inflammatory origin often contains less than 0.4% protein. More information is needed, but in general it appears that the capillary wall in the extremities retains at least 95% of the circulating protein. In man, this slight passage of protein would reduce the effective colloid osmotic pressure of the blood from 26 to 24.5 mm. of mercury, a trifling alteration. Generalizations concerning other tissues are unjustifiable because local differences occur. It is well known that the capillaries of the liver permit protein to pass very freely. Although the mesenteric capillaries of the frog are relatively impermeable to protein, those of the skin, as shown by Drinker⁵ and Conklin,⁴ allow protein to pass freely.

We have seen that the capillary wall is extremely permeable to fluid and salts, and in general relatively impermeable to the colloidal plasma proteins. Between these two extremes are a graded series of dyes whose passage through the capillary wall has been studied intensively by Rous and his associates.¹⁹ Capillary permeability to these substances is least near the arterioles and greatest in the venous capillaries and venules. The migration of these diffusible solutes, to which the capillary wall is more or less permeable, need not follow the current of water during either filtration or absorption. From present evidence the passage of these dyes is largely due to diffusion and under ordinary conditions is relatively independent of capillary pressure. Yet marked elevation of capillary pressure increases the passage of dyes everywhere along the capillary, so that under appropriate conditions the filtration of dye-stained fluid can be superimposed upon pure diffusion of dye and may even obliterate evidence of local differences in endothelial permeability. According to Peters¹⁸ the gradient of permeability to dyes does not bear upon the validity of the Starling hypothesis which deals with forces that determine the passage of protein-free filtrate as a whole through a membrane which holds back protein. The Starling hypothesis does not deal with processes which determine the diffusion of simpler solutes to which the vessel walls are permeable. On the other hand, these dye studies have shown very beautifully the manner in which diffusion, in association with a gradient of permeability, tends to equalize the distribution of simpler substances so that, as long as blood flow continues, tissue nutrition will be relatively constant even though fluid movement is grossly disturbed both in direction and rate.

Although the capillary wall is in general remarkably efficient in retaining the plasma proteins, it also loses this power very easily. Elevating venous pressure to 60 mm. of mercury produces a moderate amount of capillary filtrate containing approximately 0.3% protein. Elevating venous pressure to 80 mm. of mercury increases the amount of capillary filtrate and the protein content may be

as much as 2.8%. In these experiments capillary permeability to protein might have been increased either by simple distention or by anoxemia.

Drinker's⁵ studies in dogs have shown that lymph flowing freely during exercise contains as much as 1.5% protein. Muscular activity might increase capillary permeability by anoxemia, by increasing hydrogen-ion concentration or by changing carbon dioxide tension. The capillaries of the frog's mesentery are not affected significantly by varying hydrogen-ion concentration or carbon dioxide tension within physiologic limits, although well beyond the physiologic range the effects of injury are observed.^{11d} Anoxemia, however, increases the permeability of the capillaries in the frog's mesentery. The effective colloid osmotic pressure of the blood is reduced and fluid filters freely at capillary pressures of 5 to 10 cm. of water whereas under normal conditions these pressures are associated with absorption. The anoxemic capillary wall fails to retain the plasma proteins efficiently and the permeability to fluid is increased to 3 times normal. If anoxemia is not too prolonged these effects on permeability are reversible but prolonged anoxemia produces irreversible increase in permeability.

Gross capillary injury leads to more obvious evidence of increased permeability. The conspicuous systemic effects of widespread damage to the capillary wall were recognized clinically even before war injuries directed the attention of physiologists and physicians to the shock syndrome and its relation to the capillary circulation. The local effects of gross vascular injury may be demonstrated and measured quantitatively by studying microscopically the ultimate functional unit of the circulatory system. Certain colloidal dyes perfused through single capillaries of the frog's mesentery pass through the normal wall very slowly. If the capillary is injured mechanically by light pressure, the wall becomes highly permeable and these colloidal dyes pass rapidly through the injured area, though still retained by the adjacent normal wall.^{11b} Mechanical injury also produces "capillary stasis" in which the erythrocytes are tightly packed in the injured area, increased permeability having allowed the plasma and its contained proteins to pass through the capillary wall. Although chemical or mechanical injury increases capillary permeability so that protein passes with ease, the injured wall still retains India ink particles completely in the lumen.

The quantitative effects of gross chemical injury have been measured in the frog's mesentery, again using single capillaries. If the mesentery is covered with 50% alcohol or 1% mercuric chloride solution, fluid leaves the capillaries with extreme rapidity and at abnormally low pressures. Increased capillary permeability allows the plasma proteins to pass with ease and prevents the development of the normal colloid osmotic pressure. Fluid then

filters into the tissue spaces at a rate which is approximately 7 times normal and at capillary pressures which, under normal conditions, are accompanied by absorption. In view of this seven-fold increase in permeability the rapidity with which shock or inflammatory edema develops does not seem so extraordinary.

The normal capillary wall is impermeable to protein and the injured wall still retains minute India ink particles within the lumen of the capillary; but, nevertheless, leukocytes pass easily through both normal and injured wall. Drinker⁵ has shown that excessive venous congestion and muscular activity increase the number of red cells in lymph and yet no gross tears in the wall can be found. In the past, preformed openings in the capillary wall have been identified histologically but their existence has as often been denied.

If a frog's capillary be blocked at both ends and then an India ink suspension be injected by means of a micropipette into this closed capillary sac at pressures between 20 and 80 mm. of mercury, the ink suddenly spurts through a few isolated spots and collects in the form of minute, localized and dense collections just outside the capillary wall. Apparently the wall is not uniformly resistant but contains certain "weak areas" which under high intravascular pressure can be made to open as distinct holes through which particulate material can pass. The internal pressure required to open areas of this sort in normal capillaries of the frog's mesentery ranges from 55 to 80 mm. of mercury. In grossly inflamed capillaries pressures as low as 20 to 30 mm. of mercury have occasionally been sufficient. The openings are more numerous in venous capillaries than in arterial capillaries; they appear suddenly when pressure is sufficiently high and close abruptly when pressure is lowered slightly. The capillary wall has not been grossly torn or ruptured by the distention. As soon as the pipette is withdrawn from the capillary, circulation is resumed promptly and has been observed to continue normally for as long as an hour without stasis, deposition of platelets or other evidence of trauma. What bearing these observations may have on the mechanism of leukocytic migration is a matter for conjecture only at the present time. Chief interest attaches to the observation that the elements forming the capillary wall can be made to separate widely enough to allow India ink particles to pass without later evidence of permanent injury or grossly increased permeability to water or protein.

In the preceding discussion, I have attempted to indicate a few of the known factors which influence the movement of fluid inward or outward through the capillary wall. Normal fluid balance is, strictly speaking, not a simple balance but a complicated equilibrium resulting from the interplay of numerous forces. The pathogenesis of edema, the result of a more or less complete disruption of this equilibrium, is even more complex because gross accumulation of

fluid depends in addition upon water intake, available sodium chloride, and the renal excretion of water. However, by combining available clinical and physiologic data the factors concerned in the pathogenesis of edema may be summarized tentatively under two heads (Table 1). Those listed as primary are fundamental, since each factor in sufficient grade can itself produce clinical edema unaided by other forces. The contributory factors, on the other hand, do not themselves ordinarily produce edema, but usually modify the severity or distribution of edema produced by one of the primary causes.

TABLE 1.—FACTORS IN THE PATHOGENESIS OF EDEMA.

Factors favoring edema formation.	Clinical examples.
A. Primary:	
1. Elevated capillary pressure.	1. (a) External pressure on veins. (b) Thrombophlebitis. (c) Cardiac edema with venous congestion.
2. Lowered colloid osmotic pressure.	2. (a) Nutritional edema. (b) Nephrotic edema. (c) Cardiac edema, late stages with malnutrition.
3. Damage to capillary wall.	3. (a) Inflammatory edema. (b) Nephritic edema. (c) Cardiac edema (?), chronic anoxemia.
4. Lymphatic obstruction.	4. (a) Lymphedema. (b) Cardiac edema with venous congestion.
B. Contributory:	
5. Low tissue pressure.	5. Edema of periorbital tissues and genitalia.
6. High salt intake.	6. Increases edema if water is available.
7. High fluid intake.	7. Increases edema if salt is available.
8. Warm environment.	8. (a) Heat edema. (b) Increases all types of edema.
9. Disturbed innervation.	9. (a) Trophoedema. (b) Unilateral edema in hemiplegia.

1. The effects of elevated capillary pressure are seen whenever venous congestion is produced, whether by a tight bandage, by thrombophlebitis or by the venous congestion of cardiac decompensation.

2. Low colloid osmotic pressure of the blood is primarily responsible for the edema of prolonged protein starvation and for nephrotic edema. In advanced cardiac disease with malnutrition, mild grades of hypoproteinemia are often associated with moderate venous congestion, the resulting edema being of mixed etiology.

3. After gross injury, the permeability of the capillary wall increases seven-fold. The plasma proteins pass easily and the subcutaneous edema fluid contains from 1 to 6% of protein. This factor is the important one in the edema following burns, chemical injury or severe infection. The edema of acute diffuse glomerulonephritis is often ascribed, on indirect evidence, to slight but wide-

spread capillary damage. It has been suggested but not proved that the prolonged slight anoxemia of cardiac decompensation may increase capillary permeability and therefore be partially responsible for cardiac edema.

4. Impaired drainage of lymph, owing to congenital hypoplasia of lymph vessels, to external pressure or to recurring lymphangitis, is responsible for many unilateral collections of fluid. In addition, the edema of cardiac decompensation has been ascribed in part to obstructed lymph flow because the larger lymphatic vessels must empty their contents into congested veins.

5. Tissue pressure, as mentioned previously, is one of the factors which protects the normal human being from developing edema even when parts of the body are below heart level for relatively long periods of time. The resistance of the tissues can delay, but cannot prevent, the appearance of edema when venous congestion, capillary damage or reduced colloid osmotic pressure favor filtration continuously over long periods. The looseness of some tissues favors the early appearance of edema in certain sites where it may be recognized before being detectable elsewhere.

6. When one of the primary factors favoring edema is present, a high salt intake leads to quantitative retention of fluid, making latent edema obvious or mild edema more severe. If salt intake be restricted fluid cannot be retained and mild or moderate edema of any variety is more or less reduced. This reduction of edema by restricting the intake of sodium chloride has been advanced as evidence against the applicability of the Starling hypothesis to the problem of edema. However, it would seem more logical to regard the altered fluid balance during salt restriction as an artificial equilibrium—essentially a form of dehydration—which temporarily masks the underlying tendency toward edema formation. Certainly relaxation of vigilance as to diet is followed by return of edema, unless the underlying primary cause has been corrected. Moreover, sodium chloride restriction does not usually relieve edema due to pronounced venous congestion or a very low colloid osmotic pressure.

8. Heat produces peripheral vasodilatation, raises capillary blood pressure conspicuously and, through relaxation of capillaries, increases the area of capillary wall available for filtration. It is a matter of common observation that environmental temperature influences the volume of the extremities. Rapid fluctuations in volume are, of course, due largely to vasomotor influence but, in addition to this, slower changes in volume occur and these must be ascribed to the accumulation of tissue fluid. Patients with mild grades of edema will frequently volunteer the information that their swelling is worse in warm weather. Castellani¹ has described dependent edema in normal individuals when first exposed to the continued heat of the tropics.

9. Disturbed innervation rarely produces edema unless one of the primary factors is also operating in some degree. In cardiac patients, with latent or mild general edema, hemiplegia is followed at times by conspicuous edema of the paralyzed extremity. Lymph flow, which depends chiefly on muscular activity, is probably retarded by the paralysis. In addition, disturbances of innervation often produce temporary or permanent vasodilatation which favors filtration.

Undoubtedly other factors, in addition to those listed, will be found to play an important rôle. To mention but one example, in nephrosis a copious diuresis sometimes begins spontaneously and massive edema disappears even while the plasma proteins are still extremely low. Unravelling the mechanism responsible for this spontaneous resolution of edema may well provide a diuretic more physiologic and more constantly effective than those now at our disposal clinically.

Although investigation since the time of William Harvey seems to have penetrated well into the capillary network, our knowledge concerning the nature of the capillary endothelium is still extremely fragmentary. To judge from progress in the past 20 years, continued research will in all probability demonstrate that fluid balance is affected by additional forces concerning which we have not the feeblest conception at present. Adequate control of the elementary forces so far described will at least make the search for these other factors simpler and more productive.

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OBSERVATIONS ON BLOOD REGENERATION IN MAN.

I. THE RISE IN ERYTHROCYTES IN PATIENTS WITH HEMATEMESIS OR MELENA FROM PEPTIC ULCER.

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As shown in a previous communication,¹⁶ the rise in erythrocytes in patients with hematemesis or melena from peptic ulcer is much faster when these patients, from the first day of admission, are given a full purée diet and an iron medicament (Meulengracht treatment) than when they are submitted to the usual ulcer cure—in some cases even preceded by a few days' fasting.

But, besides a better regeneration, the time-erythrocyte curves from the patients given ample food show certain regularities which we do not see in patients on a more meager diet. To demonstrate and try to analyze these regularly occurring phenomena is the object of the present communication.

Patients. In the years 1932 to 1935, blood counts have been made on 50 patients with hematemesis or melena. These all fulfill the following requirements:

1. All patients have been given the full purée diet from the first day of admission. About three-fourths of the patients have been given iron from the first day; the rest have not received iron till some later date. These patients have not been omitted as they show the same rise as the others.

2. In all patients hematemesis or melena is supposed to be a sequel to peptic ulcer. Patients suspected of cancer, cirrhosis of the liver, Banti's disease, thrombopenia or other blood diseases—in fact, all other causes than ulcer of the stomach or the duodenum—have been omitted.

3. No patient having any known complication is included.

4. The first blood examinations have been made between 2 and 7 days after the last hemorrhage.

The patients may be divided into groups according to year of admission, first letter of name, and so forth, and the results from all these groups coincide very nicely. So we do not believe that the number of patients, even if small, is too small to show the same results that a larger number might be expected to do.

Technique. The technique has been the same as in our previous communication. The hemoglobin-standard has been 100% Hb. = 18.5% O₂. Blood for examination has been taken about once a week. During the first days—until a minimum value has been established—the blood has been generally examined more often. In about one-fourth of the patients, blood examination has been made every or every second day for the first fortnight, but the once-a-week curves agree very well with these.

Elaboration of Curves. To give an impression of the form of the curves, we have (Fig. 1) picked out those patients whose name begins with the letters L to O as a representation of the total number.

Observations. The first item for observation when such a casual group is inspected is that *in some patients the rise in erythrocytes begins at once (direct rise), while in others there is a pause or even a fall before the curve rises (indirect rise).* There may be two causes of this phenomenon: either the patients do not make up their plasma volume in the same time or there is a difference in duration of hemorrhage. Some patients may only have one hemorrhage of short duration, others may bleed for some time after admission, or have repeated hemorrhages. Both influences may be at play but there is some evidence for the latter one. In some cases a hematemesis has actually been observed during the fall in R.B.C. More indirect evidence is given in the following way: In patients whose blood has fallen to a level of less than 3 mill. R.B.C., we have for 12 patients showing a "direct" rise an average of 11.5 ± 1.0 days until the hemoglobin reaction (Gregersen benzidine test) disap-

peared from the feces. In 16 patients with an "indirect" rise (after a minimum) the corresponding time was 19.4 ± 1.4 days (a difference of 7.9 ± 1.7 days). The patients whose initial values lie between 3 and 4 millions do not show such a big difference in time of positive reaction. The average here is for 11 patients with a direct rise 15.3 ± 1.7 days and for 6 patients with a minimum 19.0 ± 3.0 days (a difference of 3.7 ± 3.5 days).

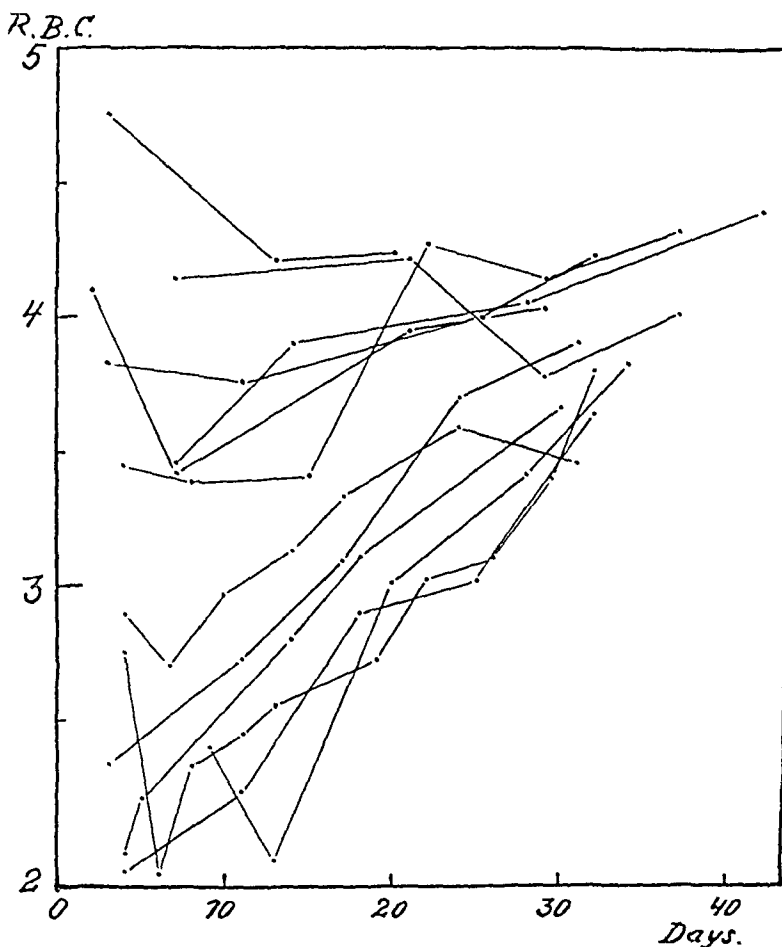


FIG. 1.—Erythrocyte-time curves from patients with names beginning with the letters L to O. Ordinate: Red blood cells in millions per c.mm. Abscissa: Days after the first hemorrhage.

Still, it must be borne in mind that the time of a positive hemoglobin test is much longer than the actual bleeding time.⁶ Whatever the cause of the fall may be, it is evident that *the rise must be reckoned from the lowest value and not from the first one.*

The patients whose counts at the beginning have not fallen below 4 millions (in all 5 patients), have shown a steady fall during the time of observation of 8 to 30 days. As no minimal value can be ascertained, these patients have all been omitted. The average

time for a positive hemoglobin test here is 13 ± 2.5 days. When first the curves begin to rise, it will be observed that *most of them are remarkably straight*.* This is not alone dependent upon scarcity of

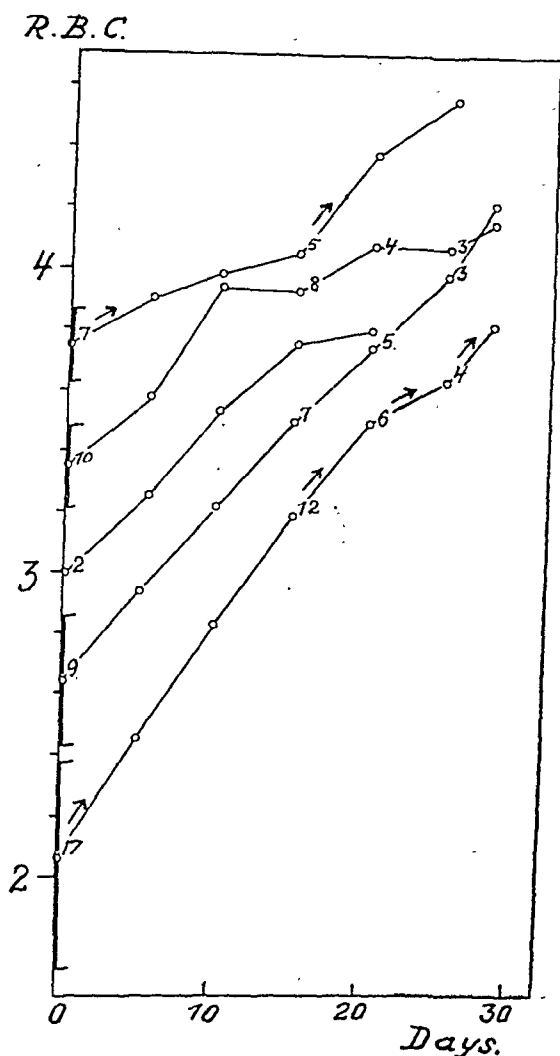


FIG. 2.—Average rise of erythrocytes, dating from day of lowest value ("individual regeneration lines"). Ordinate: Red blood cells in millions per c.mm. Abcissa: Days after lowest value has been measured. Numbers on curves: Number of patients included in respective curve.

Lines along ordinate: Range of lowest values included in respective curve.

* In our first paper¹⁶ the regeneration curves seem to be S-shaped. These curves were made as averages from 10 patients, dating from the day of hemorrhage. Some of these patients had a direct rise and some a fall at first, therefore, the average curves get a retardation at the beginning which is not found when the minimal value is the starting point.

determinations, as it is as well seen in patients examined daily as in those examined once a week.

Still another point may be seen in Figure 1: that *all curves starting from different levels tend to meet* somewhere about 40 days after the hemorrhage. We have not been able to follow the curves till normal values have been reached, as the patients have generally been discharged from hospital before that time; but in such patients which have been observed during a longer period, the erythrocyte values have not risen above this meeting point.

In order to compare the rises from different levels, one must use the lowest value as a starting point and not the initial value. In Figure 2, average curves have been made, dating from the day when the lowest value was measured.

As in Figure 1, the curves show a definite tendency to meet. This tendency may be well illustrated by plotting the average daily rise for the first 20 days against the minimal blood count (Fig. 3). Only the 34 of the 45 patients who have been followed for more than 20 days after the lowest R.B.C. value was found are included in Figure 3.

There is a distinct correlation between the minimal blood count and the daily rise in R.B.C. (Fig. 3). The more the patients have bled, the faster their blood mounts. A straight line has been drawn through the points and the difference along the ordinate between this line and the individual points (in millions of R.B.C.) has been taken as the personal error of the respective patient. The standard deviation is ± 0.012 millions R.B.C. per day. The equation of the line drawn through the points which we have termed the "regeneration rate line" may be expressed as:

$$(1) \text{ (daily rise (in millions)) } \times 33 = 4.54 - \text{ (lowest count of R.B.C. (in millions))}$$

4.54 is the point where all the individual curves tend to meet and where the regeneration rate line in Figure 3 cuts the abscissa; 33 is the number of days required to reach this point. This number is denoted by the inclination of the regeneration rate line. We think an explanation of the phenomena here observed: the straightness of the lines and the tendency to meet, may be found in the following theoretical considerations.

Theory for the Mechanism of Regeneration. *Normal regeneration rate.* We will suppose first that the hemorrhage in no way interferes either with blood production, or with blood destruction nor longevity of new-formed or old erythrocytes. It is assumed that the red corpuscles live under normal conditions somewhere between 20 and 50 days. We know that normally the production and destruction of erythrocytes balance each other in such a way that the number is kept constant at about 5 millions per c.mm. in women and 5.5 millions in men. ("Hemolytopoietic equilibrium" of Krumbhaar.)

With a life-span for the red corpuscles of 25 days, this means that out of 5 million cells, every day approximately 200,000 are destroyed to be replaced by 200,000 new-formed cells. If now a patient with a normal count of 5 millions R.B.C. in 1 day loses half his blood (and has no subsequent bleeding) he will—after correction of volume—have 2.5 millions left. The hemorrhage has taken place without any selection of the blood lost: thus the 2.5 millions left behind represent as well corpuscles formed the day before as those standing upon the threshold of destruction. The 2.5 millions therefore will

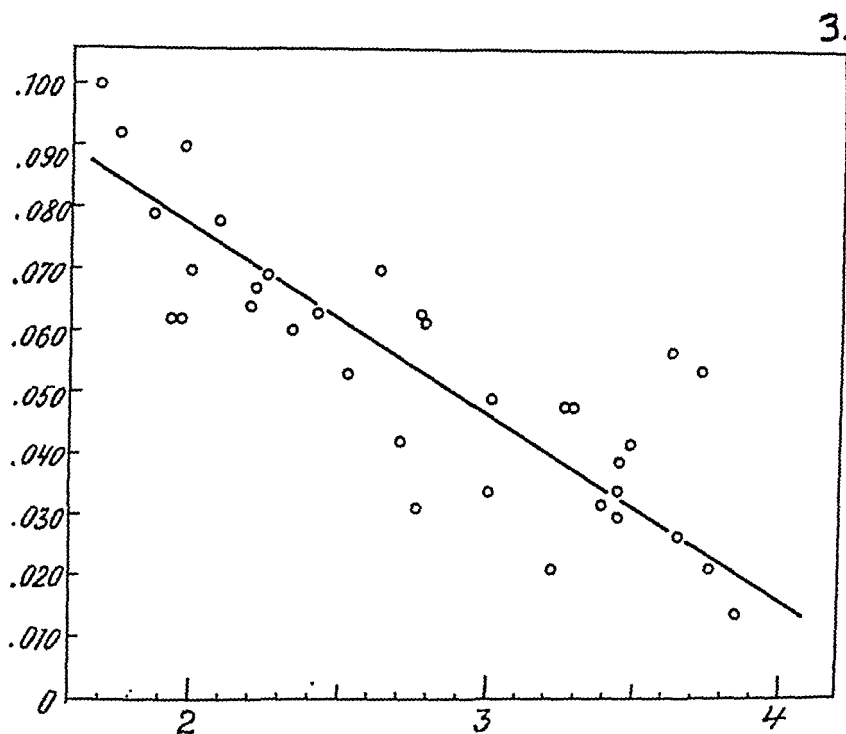


FIG. 3.—Average daily rise in erythrocytes during the first 20 days after the day of lowest erythrocyte count, plotted against this value. Ordinate: daily rise in millions of red blood cells. Abscissa: lowest erythrocyte count. Each point corresponds to 1 patient. The line is drawn as an average ("regeneration rate line").

disappear in the course of 25 days: every day 100,000 will be destroyed. But if the normal production of 200,000 still goes on, there will be a surplus of 100,000 corpuscles daily: in 25 days 2.5 millions. Thus the normal count of 5 millions will be reached at this date; the regeneration will be complete and the balance restored, the product of 200,000 from the first day after hemorrhage now being ripe for destruction. It will be seen (Fig. 4) that the curves of regeneration according to this theory are represented by straight lines, even if it might be expected that they will bend some-

what on nearing the normal level. The batch of erythrocytes from a single day probably do not all have the same longevity; the 25 days are an average and the greater destruction which is to appear 25 days after the hemorrhage will begin to be felt a while before. The straightness of the individual curves was one of the points observed above.

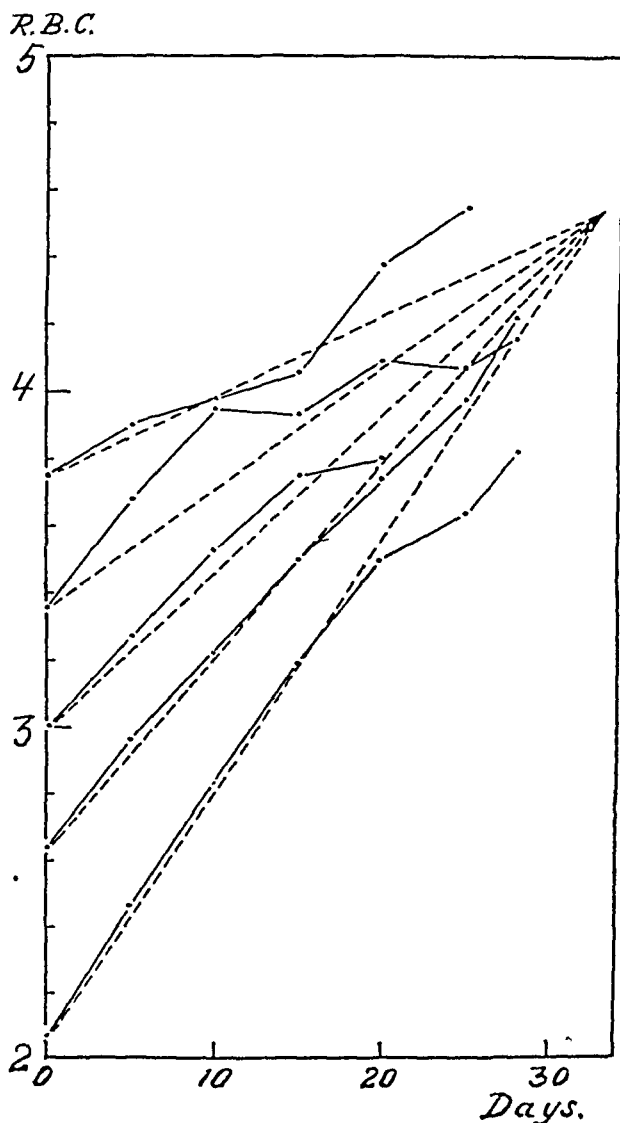


FIG. 4.—Found average rise of erythrocytes compared to theoretical lines. Ordinate: Red blood cells in millions. Abscissa: days after lowest erythrocyte count. Full lines: found average values (from Fig. 2.) Dotted lines: Values obtained from application of theory.

The mechanism of regeneration sketched here involves another of the points observed: namely that the curves will reach the same point in the same time. No matter what number of R.B.C. have been left after the hemorrhage, all of them will be destroyed in the

course of the lifetime of the last-born erythrocytes, to be replaced by the normal number of new cells formed within the same time. With the figures used in the first example: 5 millions R.B.C. with a life-time of 25 days as normal, a patient bled down to 1 million will destroy 40,000 a day, and with a production of 200,000 he will have a daily surplus of 160,000, thus making up the deficit of 4 millions in 25 days. In the same way, a patient who has 4 millions left will have a daily destruction of 160,000 and a surplus of only 40,000, thus using absolutely the same time for completion of his blood count as the patient who has lost four times as much blood.

This theory may be summarized in an equation:

$$(2) \cdot (\text{daily rise}) \times (\text{longevity of cells}) = (\text{normal value}) - (\text{lowest value}).$$

As will be seen, (2) is very similar in form to (1), only in (1) instead of normal level another value has to be inserted which we have termed "end point of regeneration" because the cells in our patients do not seem to rise any higher, at least for a time. If (2) is altered into:

$$(2a) (\text{average daily rise during a definite time}) \times K = (\text{end value of regeneration}) - (\text{lowest value}),$$

an equation of the form (1) will be covered by it. K in (2a) is a constant. It cannot in all forms of regeneration be supposed to give the life-time of the erythrocytes.

(1), (2) and (2a) are only valid for a time not longer than the life-time of the erythrocytes. Thus we have found that the equation extracted from our experimental findings is very similar in form to the equation which results from our theoretical considerations.

In Figure 4, we have repeated the average curves from Figure 2, and with dotted lines entered the lines of regeneration which result from an application of the considerations just evolved, using 4.54 millions as an end point of regeneration and 33 days as the life-time of the red cells (or K in 2a).

As a preliminary result of our investigations, we may state that a set of theoretical lines cover the found values quite well. There is, indeed, a slight difference between the end point of the theoretical normal regeneration and that which we have found in our patients. Still, we think, the approximation is so good that we may continue our investigation along the lines entered upon.

We are well aware that the time-erythrocyte curve is influenced by many factors and cannot *a priori* be taken as a sole and true picture of the rapidity of regeneration. We have registered as many of the influences coming into play in this respect as we could imagine.

Factors Influencing the Time-erythrocyte-curve During Regeneration After Hemorrhage:

- A. Continued bleeding.
 - B. Alterations in total blood volume.
 - C. Daily destruction of red blood cells.
 - D. Daily output of red blood cells depending upon: *a*, size of bone marrow; *b*, intensity of work of bone-marrow; *c*, reserves of ready-built corpuscles; *d*, reserves of material for hemoglobin and stroma building; *e*, supply of new material, its resorption and further elaboration.
 - E. Longevity of old and new-formed erythrocytes.
 - F. Individual normal level and other individual characteristics.
- Factors A and B will have a more indirect influence upon the apparent regeneration as expressed by the time-erythrocyte curves, C, D and E will be most important as the essential factors of regeneration.

The influence of *prolonged bleeding* we think we have eliminated as far as possible by taking the lowest values. We cannot at present come any nearer to a solution of this question. The next point is the *blood volume*. It has been shown several times that at least the plasma volume is made up very quickly after a hemorrhage, in fact within hours. (Boycott and Douglas¹ (where older literature is reviewed), Keith,¹⁰ Hirota,⁷ Camero and Krumbhaar,² Robertson¹⁴). Some authors even have observed an overdilution. In the case of a very big hemorrhage (down to a hemoglobin per cent of about 20), the blood is not diluted at once; it seems there is a mechanism to prevent a fall of hemoglobin below this cipher (Robertson and Bock¹⁵). Blood losses of this order of magnitude have not been met with in our patients (min. Hg%: 35). In shock, too, the plasma volume is not made up. We do not have the impression that any of our patients have had shock of any great duration. The rapid restoration of the plasma volume especially takes place if the patients are given much fluid *per os* (von Limbeck,¹² Robertson and Bock¹⁵). This, indeed, has been the case in our patients (Meulengracht,¹³ Schiødt¹⁶). We have nevertheless taken the precaution not to include blood counts from an earlier date than 24 hours after the last hemorrhage.

Robertson and Bock, in man, and Camero and Krumbhaar, in the dog, have shown, that even if the plasma volume is made up at once, the total blood volume is not, the corpuscle volume remaining diminished in proportion to the deficit in number. A correction for this factor might be introduced into our computations, but it would make no alteration in the main fact: that all the curves from different level tend to meet in one point.

Destruction, Production and Life-length of Cells. It is evident that there must exist an interrelation among these three factors. If blood corpuscles live rather independently and die at a certain age—as any other biological population—an increase of destruction might be imagined to happen in two ways. Either, the cells might die at an earlier age than before or there might be instituted a new form of extra destruction in such a way that every day a certain

number of corpuscles were destroyed independent of their age. The latter mechanism, too, would mean a diminution in average life-time of all cells. Still, it would be most natural to reserve the term: shortening of life-time for the first mechanism and increase of destruction for the second one.

Another theory, which perhaps has not been openly expressed, but which is tacitly involved by many assumptions about regeneration, supposes the second mechanism to be the normal one. In this way, destruction would be an active function of the organism. Among the cells destroyed every day all ages would be represented in proportion to their number. The average life-time of the cells would be a passive function of the number present, the daily production and the daily destruction. In this way, the longevity in the more active sense of the first theory would be of no interest and could possibly be omitted from calculations on regeneration.

Let us look into the consequences of these theories. The first is the one we have followed in our previous theoretical considerations.

According to this theory, anemia might be a sequel to either diminution of production, increase of destruction or shortening of the life-time of the red corpuscles. (In the latter case, erythrocytes might be imagined to be born with less resistance to age than normally.) With the figures used in our previous numerical examples, a blood level of, for example, 4 millions might as well be the result of a daily production of 160,000 instead of 200,000, or an extra destruction or loss of 40,000, or a shortening of the life-time of the erythrocytes from 25 to 20 days. In all cases there would be an equilibrium between production and destruction at 4 millions. Factors which produce anemia will affect regeneration in the same way if they still are active. Regeneration, indeed, might happen in two ways. Either the noxious influence would fall away—and then regeneration must be assumed to follow the rate for normal blood exchange—or a normal blood level might be reached by the introduction of some compensatory mechanism, for example, an increased production. In most anemias, we do not yet know which way is followed.

It might to some extent be possible to see from the regeneration curves which factors were implied. If, as a sequel to hemorrhage, or to the disease which caused hemorrhage, the daily production were 160,000 instead of 200,000, the blood corpuscles would reach a level of only 4 millions (as long as production stayed low); but this level would be reached in the course of the normal life-time of the red cells, 25 days (if this factor were not altered by the hemorrhage). On the other hand, if the average life-time of all red cells were shortened to 20 days, we should reach the same level but in 20 days. In the case of increased destruction the question, as mentioned, has two sides. If only the oldest corpuscles were destroyed, we should not be able to discern this mechanism from the shortening of the

life-time. On the other hand, corpuscles might be destroyed or lost without respect to age. This might be imagined, if, for example, hemorrhage continued at a constant rate. The consequences of such a mechanism could only be demonstrated with the help of rather intricate mathematics. An equilibrium should not be reached within the life-time of the erythrocytes.

These considerations may be applied to our curves. It will be seen at once that when the normal life-time of the red corpuscles is not known, it will be impossible from either of the theories named to see why a set of regeneration curves do not reach normal level. The fact that in our patients only 4.54 millions is reached might thus as well be due to a shortening of the life-time from 39 to 33 days as to a minus in production (or a plus to destruction) of about 25,000 cells a day. This would mean a difference from normal of minus 15%. (As our group of patients consists of 9 women and 25 men, 5.37 would be the average normal level. This number has been the basis of the preceding computations.) Still, even with a possible variation from 33 to 39 days, this way of finding the life-time of the erythrocytes is not more insecure than other methods. The longevity found by us is well in accordance with the results of most of these. If patients with hemorrhage could reach normal level at once, we possibly should be able to come nearer to the point. In this case, the time for regeneration would correspond to the average normal life-time.

When the normal life-time were known, we should be able to exclude changes in longevity as a cause to abnormal regeneration. Increased production might be evidenced by reticulocytosis, increased destruction by increased plasma bilirubin or by increased excretion of urobilin.

Check and Stimulus. The rate of regeneration can be affected by changes in production, life-time or destruction of cells. Decrease of production, shortening of life-time or increase of destruction will be felt as a check, the reverse as a stimulus. From regeneration curves, we can only see the effect—check or stimulus; the cause—an alteration in production, life-time or destruction—can only be shown by indirect evidence. Combinations may be imagined, for example, increase of both production and destruction. In such a case only the stronger of the two would be felt. We have demonstrated that at normal blood-exchange rate, the normal blood level would be reached within the life-time of the erythrocytes. This has been formulated in equation (2). But in this case, *any stimulus*—and by a stimulus we could only mean any factor which would increase the daily surplus of cells—*would invariably result in the normal level being surpassed*. When normal rate gives normal level, we should in the case of a stimulus get an extra number of cells which would give a higher level. So far as we know, a rise above normal values has only in a few cases been met with in regeneration after

anemias. Therefore, we have to admit of two possibilities: either normal blood-exchange rate may account for regeneration, or, in the case of a stimulus, an extra mechanism must be introduced to account for the fact that normal level is not exceeded. In some anemias, we have assumed that a noxious influence is still present in spite of regeneration. This would account for the fact that normal level is not surpassed. But in the case of regeneration after a hemorrhage which has stopped, we could not assume the existence of a stimulus without at the same time supposing a shorter life time or an increased destruction with rising blood counts. The latter theory has been adopted by Escobar and Baldwin.⁴

How such a mechanism might be supposed to act depends on several factors. First, it would depend on the nature of the stimulus. It would be most natural to suppose that the stimulus is a function of the magnitude of the blood loss, linear, logarithmic or exponential. The stimulus, once started, might exist through the whole range of regeneration. In order not to exceed normal level, the regeneration at this point would have to be interrupted by a check of such a magnitude that the surplus was exactly neutralized. It would be more natural, however, to suppose that the stimulus would diminish with rising blood counts in such a way that at a given moment it would be a function of the immediate erythrocyte count and not of the lowest one. But here, even with a linear correspondence of stimulus to blood count, we might expect individual regeneration curves which were not straight. We should find curves rising steeply at first and slowing down gradually until they approached a final level asymptotically. This mechanism might be compared to an increasing check. Only this check must mean more than a diminution of stimulus. It must indeed be active, that is, bring the rate lower down than normal, for only by the existence of such a check can a transgression of normal level be avoided. A stimulation of one part of the curve must invariably be followed by a check upon the latter part of it.

Anyhow, our theory of a normal regeneration rate after hemorrhage seems much more natural. The straightness of our individual regeneration lines speaks against stimulus and check as functions of the immediate blood counts. There might be a stimulation of regeneration in our cases but then it would have to be uniform through the whole range of regeneration. Besides, there would have to be a check coming into play at normal level. Only this mechanism would be able to explain straight individual regeneration lines.

All this seems much more complicated than necessary when in fact all characteristics of the regeneration lines can be explained by the assumption of a normal regeneration rate.

The existence of a check, on the other hand, is easy to demonstrate, as in this case the regeneration curves should not reach normal level. When the check was of the same magnitude through

the whole range of regeneration, the lines still would be straight. But a check might be a function of the blood loss in the same way as a stimulus. In this case, the individual regeneration curves (if the check were not so great that there was no regeneration at all) would bend the other way: they would start slowly and then rise.

Discussion. In our patients we have found a slight check. This is evident because the end point of regeneration is not normal level. How long the patients remain at this lower level is not clear; one month after discharge some patients do not yet give normal counts. The idea of a check, too, is supported by the behavior of the regeneration lines from patients starting from values above 4 millions. As mentioned, these patients show a fall, especially those coming from values above 4.60. As has been shown in a previous section, the size of the check can be assumed to be about 15% of the normal blood exchange rate. Its nature cannot be made quite clear till we know the figure for the longevity of the erythrocytes better. From our individual regeneration lines and from the regeneration rate line, it can be seen that the check seems to be of the same size during the whole time of the regeneration and at all blood values.

Even if we have to abandon the idea of a stimulus upon regeneration, still, we cannot deny that there is evidence of an increased marrow activity, such as reticulocytosis, nucleated red cells, leukocytosis. The percentage of reticulocytes seems to be a function of the magnitude of the blood loss (Robertson and Bock¹⁵). But this increased production must be balanced by a check, and the check must be the stronger of the two. If stimulation and check balanced each other exactly, the result would be a normal regeneration rate; here, we get a 15% deficit.

Another explanation of the reticulocytosis might be the throwing out of a reserve. If the longevity of such a reserve were not another than for normal cells, it would not alter the regeneration curve, only its starting point. Generally, to be sure, such phenomena as reticulocytosis, and so forth, have been interpreted as signs of increased marrow activity.

A check of the sort found in our patients might be imagined if the treatment were not fully sufficient.* Perhaps, then, a still more intensive treatment ought to be given to these patients. This might consist in a food more rich in vitamins or in administration of a liver preparation. This last point, indeed, has been suggested several times and it has been shown to be effective in regeneration after hemorrhage (Cheney and Niemand,³ and Gram⁵).

* Another factor producing a check might be the administration of alkalis. This has been shown by Kellogg and Mettier (*Arch. Int. Med.* 58, 278, 1936) to inhibit utilization of dietary iron in the regeneration of hemoglobin in patients with peptic ulcer. Our patients up till now have been given equal amounts of bicarbonate of sodium and subcarbonate of magnesia with 3% of extract of *hyoscyamus* one teaspoonful 3 times a day. This medication now has been discarded.

Concluding the discussion of our clinical data and theoretical considerations, we must state that in patients with hematemesis or melena from peptic ulcer, treated with the Meulengracht cure, *the essential points in regeneration can be explained as a natural sequence to maintenance of a practically normal blood exchange rate.*

Without doubt our theoretical considerations may be applied to other forms of anemia.

Literature. We have not been able to find much in the literature about the rate of regeneration. Hunter,⁹ however, in 1886, was very near to making the same assumptions that we put forth here. In the handbooks, even up to quite recent dates, we find stated that a heavier blood loss demands a longer time for regeneration than a smaller one. Hirschfeld,⁸ for instance, says: "The duration of the regeneration depends on the severity of the blood-loss and the individual peculiarities of the organism as well as on the therapeutic measures." This conception of the mode of regeneration implies the idea of a check; the severity of the check conforming to the magnitude of the blood loss. In fact, we have seen this mode of regeneration in patients with hematemesis and melena treated with fasting and ulcer cure. This will be more elaborately detailed in a following paper. This idea of the regeneration seems to have prevailed, no doubt, because most conceptions of acute posthemorrhagic anemias in man rest upon studies of hematemesis or melena and postoperative anemias, and these generally have been treated with the ulcer cure or similar diets.

Practical Application of Theory. Besides giving an idea of the mechanism of regeneration, we think our way of expressing the rise in erythrocytes by a simple equation may be used as a standard for estimating the rise in individual cases. The same thing already has been done by Gram.⁵ He expresses the regeneration rate as the percentage of deficit in hemoglobin regained during the first 10 days after admission. The deficit is defined as the normal minimum for the sex minus the first determination after admission. If this manner of proceeding has any justification, the regeneration rate expressed in this way must be a constant in patients having received the same treatment, independent of the size of the hemoglobin loss. Gram's expression, then, can be formulated as

$$(3) \quad \frac{10 \times (\text{daily rise}) \times 100}{(\text{normal minimal value}) - (\text{value on admission})} = K$$

This equation will be seen to be identical in form with our (2a):
(2a) (average daily rise) $\times K = (\text{end value}) - (\text{lowest value}).$

Gram's expression is very handy for daily use but it does not imply anything that is not found in our equation too. Besides we think that 10 days is too short a time and ought to be replaced by a longer one, and we should here suggest 20 days. Finally Gram does not take into account new bleeding subsequent to admission.

Summary. Erythrocyte-time curves are given for 50 patients with hematemesis and melena from peptic ulcer. These patients

have been given the Meulengracht treatment, a full purée diet from the first day of admission; most of them have received iron too. The individual curves seem remarkably straight. Starting from different levels, they tend to meet in one point, 4.54 millions R.B.C., 33 days after the lowest erythrocyte value was measured. This is strictly in conformance to a theory for the regeneration, based upon the assumption of maintenance of normal blood exchange rate, which can be expressed by the equation:

$$(\text{average daily rise}) \times (\text{longevity of erythrocytes}) = (\text{normal value}) - (\text{lowest value}).$$

This theory has been discussed at length. In our patients a slight check has been demonstrated which may be explained by the assumption of a 15% diminution in production rate.

The figure for the longevity of the erythrocytes, found in our patients, 33 days, is well in accord with the results from other methods.

The practical applicability of our equation has been discussed.

The author wishes to acknowledge his indebtedness to G. Rasch, Ph.D., for valuable assistance in statistical and mathematical treatment of this problem. A mathematical exploration of our theory by Dr. Rasch and the author will be forthcoming. Miss Lundgren and Miss Norman-Hansen have given technical assistance.

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OBSERVATIONS ON BLOOD REGENERATION IN MAN.

II. THE INFLUENCE OF SEX, AGE, FORM OF HEMORRHAGE, TREATMENT AND COMPLICATIONS ON ERYTHROCYTE REGENERATION AFTER HEMATHEMESIS AND MELENA FROM PEPTIC ULCER.

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IN a previous communication² we have found that the daily rise in erythrocytes in patients with hematemesis or melena from peptic ulcer is dependent on the degree of anemia. This has been expressed

by an equation: $R \times 33 = 4.54 -$ (lowest erythrocyte value [in millions]). (R is the daily rise in erythrocytes [in millions] during the first 20 days after the lowest value was found.) It was suggested that this equation might be used as a standard when the influence of factors like age, sex, and so forth are to be examined. Without such a standard, only patients bled down to the same level might be compared, as in our first paper on the rate of regeneration as influenced by treatment.¹ The individual deviation from the standard has been expressed as the difference in daily rise (in thousands of R.B.C.) between the value found and the average value for the corresponding minimal erythrocyte count derived from the equation. The normal average values which form the basis of the equation have been made out from examination of 34 patients without any known complication, dating from different years. All these patients have been given a full purée diet from the first day of admission. The rise in erythrocytes has been reckoned from the lowest value found. The standard deviation in these patients was 12 (thousands of R.B.C.). The data from these 34 patients have been tabulated in Table 1. In Figure 3² will be found a graphic representation of the equation and the deviations of the 34 patients tabulated here.

In the present paper, the influence of sex, age, form of hemorrhage, treatment and complications will be examined. All erythrocyte time curves from individual patients have been treated in the same way, that is, the lowest erythrocyte value has been used as a starting point and the rise in red cells during 20 days after the day of lowest value has been taken as a measure for the rate of regeneration.

Influence of Sex. Among the 34 patients are 9 women and 25 men. The average deviations from the line are -3.2 and $+1.02$, respectively; the difference 4.22 is only $1.1 \times$ the mean error.

Age. The deviations are plotted against age in Figure 1. It will be seen that patients between 20 and 40 do not regenerate their blood any better than do patients between 40 and 60. Above 60 we have only 2 patients, below 25 likewise 2.

Form of Hemorrhage. Seventeen patients (3 women and 14 men) have had melena, 17 (6 women and 11 men) both hematemesis and melena. Patients with hematemesis do not average a lower blood count than patients with melena (average minimal values 2.75 and 2.80). The average deviation from the standard regeneration line is $+2.35$ for the melena group and -2.35 for the hematemesis group. The difference is too slight to be of any significance, being about the size of the mean error. This is quite remarkable; one might perhaps have expected a better regeneration in patients with melena only, as these at least have a theoretical possibility of regaining some of the lost blood through absorption during the passage down the intestinal tract. There is other evidence that such an absorption does not take place to any great extent. On microscopic

examination of the feces from patients with melena, one finds innumerable "ghosts" and even apparently intact red corpuscles.

TABLE 1.—PATIENTS ON MEULENGRACHT TREATMENT.

Pt. No.	Sex.	Age.	M. H.	Min. val.	20 d. val.	Daily rise.	Deviation.	Days + Bz.	Day Fe.	Dir. ind.
1	M	33	M.	1 69	3 68	100	+13	27	1	i.
2	M	58	H.	1 77	3 60	92	+ 8	23	1	i.
3	F	30	H.	1 87	3 44	79	- 2	20	2	i.
4	M	34	M.	1 93	3 16	62	-18	29	1	i.
5	F	40	M.	1 94	3 17	62	-17	13	2	d.
6	M	51	M.	1 97	3 76	90	+12	17	1	i.
7	F	49	H.	2 0	3 39	70	- 7	13	1	d.
8	F	56	H.	2 09	3 64	78	+ 3	20	2	i.
9	M	37	H.	2 20	3 48	64	- 7	21	1	i.
10	F	17	M.	2 21	3 54	67	- 4	9	4	d.
11	M	33	H.	2 23	3 60	69	- 1	15	7	d.
12	M	27	M.	2 34	3 63	65	- 2	5	1	d.
13	F	30	H.	2 42	3 67	63	- 1	25	1	i.
14	M	23	H.	2 52	3 58	53	- 8	16	1	d.
15	F	25	M.	2 62	4 02	70	+12	16	1	d.
16	F	50	H.	2 70	3 53	42	-14	9	1	i.
17	M	53	M.	2 76	4 0	62	+ 8	23	13	i.
18	M	66	H.	2 76	3 38	31	-23	14	1	i.
19	M	42	H.	2 77	4 0	62	+ 8	15	1	i.
20	M	54	M.	3 0	3 68	34	-13	17	1	d.
21	M	33	M.	3 0	3 97	49	+ 2	20	1	d.
22	M	49	M.	3 21	3 62	21	-19	10	12	d.
23	M	32	M.	3 25	4 20	48	+ 9	13	1	d.
24	M	43	M.	3 25	4 20	48	+ 9	11	1	d.
25	M	54	H.	3 39	4 02	32	- 3	9	1	i.
26	F	30	H.	3 44	4 12	34	+ 1	32	1	i.
27	M	28	M.	3 44	4 04	30	- 4	20	4	d.
28	M	54	H.	3 45	4 23	39	+ 5	22	1	d.
29	M	54	H.	3 48	4 32	42	+10	15	.	d.
30	M	49	M.	3 61	4 68	54	+23	19	4	d.
31	M	34	M.	3 65	4 19	27	= 0	14	1	d.
32	M	55	M.	3 72	4 80	54	+28	20	1	d.
33	M	80	H.	3 76	4 19	22	- 2	19	11	i.
34	M	55	H.	3 85	4 13	14	- 6	26	1	d.

M = melena alone; H = hematemesis and melena. The lowest erythrocyte value found is given in millions per c.mm., also the value found 20 days later. In the next column is given the average daily rise in red blood cells during these 20 days in thousands of red blood cells, and under "deviation" the difference between this value and the average rise as found from our equation, likewise in thousands of red blood cells. Under "Days + Bz" is given the number of days from the beginning of the hemorrhage until a negative benzidine reaction has appeared in the feces.*

* Meulengracht (Acta med. Scand. Suppl., 59, 375, 1934) reckons the time for a positive benzidine reaction from the day of admission, and not from the day of hemorrhage.

Then is found the day after admission on which iron was begun and in the last column is indicated whether the lowest value found was the first one (direct rise: d) or was found later as a minimum value and the rise thus an "indirect" one (indicated by: i).

Whipple and Robscheit-Robbins,³ too, have shown that in experimental bleeding anemia in dogs, hemoglobin by mouth is not more effectual in promoting regeneration than other protein. It is well known that even very small volumes of blood ingested (down to 5 cc.) give a positive benzidine reaction in the feces. This would

hardly be the case if blood were digested and absorbed to any great extent.

Treatment. A. Iron. Eleven out of the 34 patients were not given iron from the first day of admission. Only 5 of these had been in hospital more than 1 week until iron was given. The deviations for those patients are: -1 , $+9$, -19 , $+10$, -1 (average -0.4). As the largest deviation is only $-1.6 \times$ the standard deviation, there does not seem to be any retardation of the regeneration. Of course no definite conclusion about the influence of iron can be drawn from such a limited number of patients, but we have felt justified in including them.

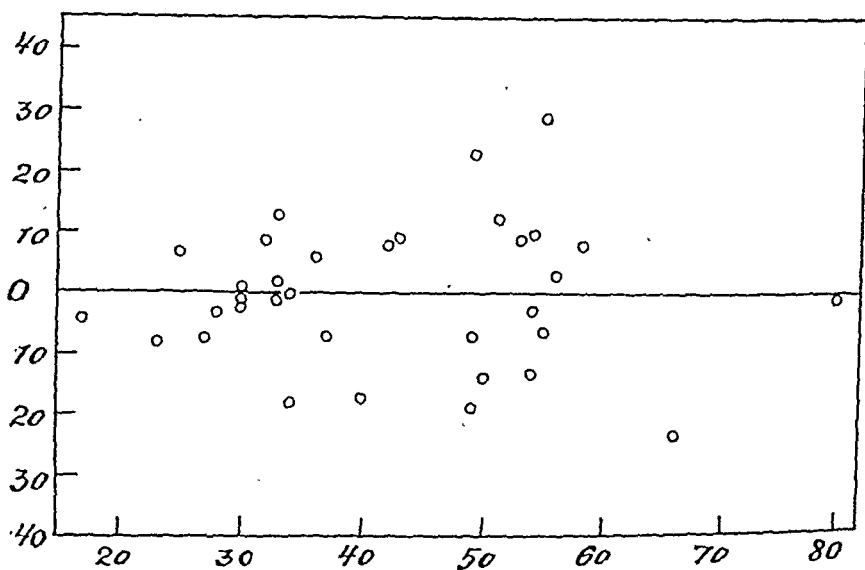


Fig. 1.—Deviation from average in relation to age. Ordinate: Deviation in thousands of red cells. Abscissa: age of patient. Each point corresponds to one patient.

B. Fasting and Ulcer Cure.—As already shown in another way,¹ we have found a very pronounced difference between “ulcer cure” and “purée diet” in their influence upon regeneration. There is a difficulty in treating the curves of patients on ulcer cure in the way used in the present paper because a fall often keeps on for a very long time—in some cases, indeed, until the patients are given the purée diet, that is, about 28 days after admission. The counts of no patient on purée diet from the first day began to rise later than seventeen days after the last hemorrhage. In this way the establishing of a minimal value for some of the patients on ulcer cure is impossible. When only patients showing a rise are included, the ulcer cure gets an undue advantage. Nevertheless, it will be seen from Figures 2 and 3 and Table 2 that there can be no doubt about

TABLE 2.—PATIENTS ON ULCER CURE.

Pt. No.	Sex.	Age.	M. H.	Min. val.	20 d. val.	Daily rise.	Deviation.	Days + Bz.
35	M	24	H.	1.21	1.38	9	(-92)	23
36	M	58	H.	1.28	2.12	42	(-17)	17
37	M	62	H.	1.66	2.27	31	-57	19
38	M	35	M.	1.92	2.46	27	-53	19
39	M	34	H.	1.93	1.99	3	-77	16
40	M	48	M.	2.21	2.93	36	-34	10
41	M	53	H.	2.29	3.28	50	-18	26
42	F	45	H.	2.40	2.97	29	-36	43
43	F	39	H.	2.47	3.09	31	-13	
44	F	43	M.	2.68	2.97	15	-41	18
45	M	59	M.	2.68	2.98	15	-41	27
46	F	45	H.	3.13	3.40	14	-28	
47	M	56	M.	3.21	3.90	35	-5	11
48	M	33	H.	3.31	3.97	33	-4	8
49	M	31	M.	3.52	3.72	10	-20	44

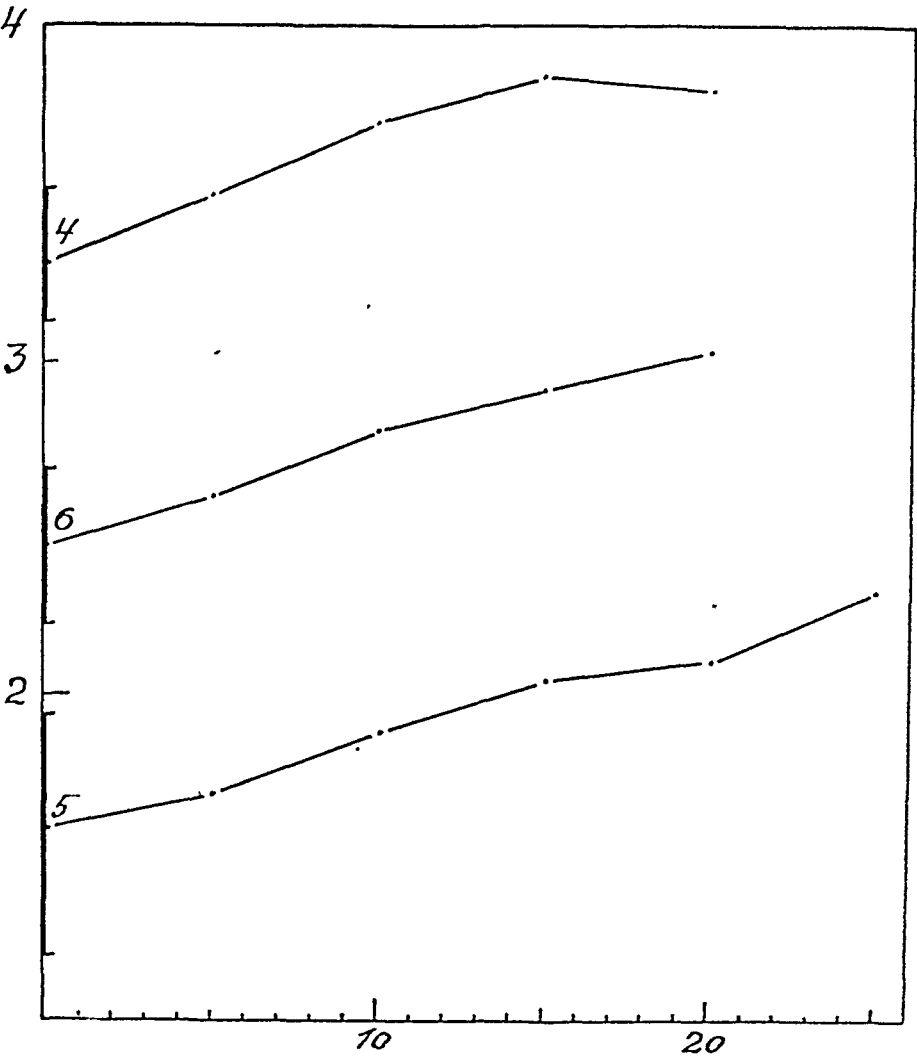


FIG. 2.—Average individual regeneration curves from patients on ulcer cure. Ordinate: Red blood cells in millions. Abscissa: Days after a minimum erythrocyte value was reached. Lines along ordinate: Range of minimal values included in respective curve. Numbers on curves: Number of patients included in respective curve. All curves have been interrupted when patients were given the jejunic diet.

the great difference between the two treatments. In Figure 2 will be seen average regeneration curves from 15 patients on the ulcer cure. The patients have been divided into three groups, starting from different levels. It will be seen that the rise from these levels is nearly parallel; patients with a large hemorrhage and a corresponding low minimum level demand a much longer time for regeneration than patients starting from a higher level. This corresponds to the older conception of the manner of regenera-

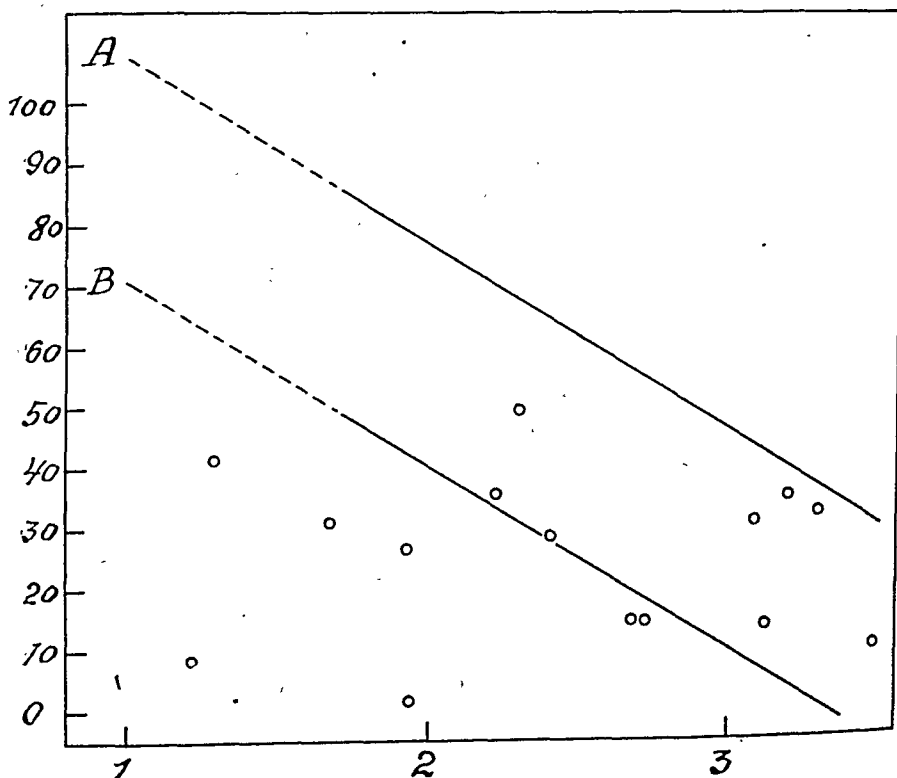


FIG. 3.—Rise of patients on ulcer cure. Ordinate: Daily rise of red blood cells in thousands during the first 20 days after lowest value. Abscissa: lowest red blood cells in millions. Line A: Average for 34 patients on purée diet from first day of admission (partly extrapolated). Line B: Distance of three times standard deviation from A.

tion after hemorrhage.² But from the corresponding curves in the same paper² (Figure 2), it will be seen that patients on the purée diet regenerate their blood in a strikingly different manner; here, all curves tend to meet and patients from a low level regenerate their blood as fast as patients from even the highest levels. As evidenced in this paper,² this corresponds to our conception of a normal regeneration rate. The patients on the ulcer cure, then, show a form of regeneration very far from normal. In fact, the

parallelism of the regeneration lines indicates that there must be a check of considerable size and that this check must conform to the magnitude of the blood loss: the more the patients have bled, the greater is the check.

The same is seen in Figure 3 where the individual daily rise in patients on ulcer cure during the first 20 days after the minimal erythrocyte value was reached has been plotted against this value. The average line drawn through the corresponding findings from patients on the purée diet has been included and the difference both in manner of regeneration and rapidity of rise in the two treatments is clearly seen. No patient on the ulcer cure reaches the average for the patients on the purée diet (Line *A* in Figure 3) and only half of them are above Line *B*, drawn in the distance of three times the standard deviation from *A*.

Three of the 15 patients here included have fasted for a few days (being given ice-pills for thirst), but they have all had very little food and drink for the first week. The ulcer cure in this hospital at the time when these patients were treated (1929-1931) started with $\frac{1}{4}$ liter of tea and nothing else, the next day was added $\frac{1}{4}$ liter of oatmeal soup. One or 2 days after was added another $\frac{1}{4}$ liter of oatmeal soup and again 1 or 2 days later $\frac{1}{2}$ liter of milk.

Thus the patients were deprived both of drink and food. The check mentioned is not only prolonged bleeding. The feces of 13 of the 15 patients on ulcer cure had a positive benzidine test for 21.6 ± 3 days. The average for the patients on Meulengracht treatment is 17.6 ± 1.04 ; the difference is not significant, being only $1.3 \times$ the mean error.

Transfusion. A third factor in the treatment besides diet and iron is blood transfusion. As only 5 patients who have been given blood transfusion have been followed long enough to get a curve of the rise in erythrocytes, the number is too small for any definite conclusions. Two of the patients, furthermore, have bled down so low (0.87 and 1.58 million, respectively) that we have no patients for comparison. But 3 patients with starting values between 2 and 3 millions do not differ from the patients who have not been given a transfusion. The data are given in Table 3:

TABLE 3.—PATIENTS GIVEN TRANSFUSION.

Pt. No.	Sex.	Age.	Min. val.	Daily rise.	Deviation.	Remarks.
50	M	37	0.87	112	+ 1	From extrapolated average line.
51	F	18	1.58	37	-53	
52	F	53	2.25	69	± 0	
53	M	41	2.39	82	+17	
54	F	53	2.55	70	+10	

The minimum values here are the lowest (and in all these cases the first blood count after transfusion. All patients have been given purée diet. The patient with a deficit of 53,000 red blood cells per day had 4 severe hemorrhages and was given 3 transfusions. She did not seem to have any complications but she was very delicate and frail. This patient is the only one in this group who has not been given iron. The other patients only had 1 transfusion. The findings are seen in Fig. 4.

Blood transfusion in these 5 cases has not shown any definite efficiency in promoting regeneration. We find it quite remarkable that these patients show the rises expected from comparison with our standard patients.

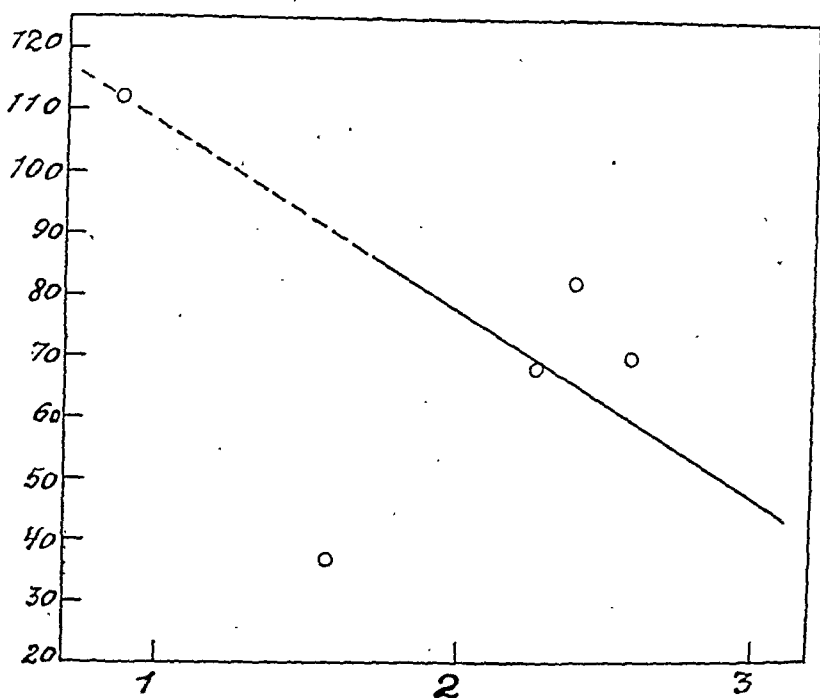


FIG. 4.—Rise in patients given blood transfusion. Ordinate: daily rise in thousands. Abscissa: lowest red blood cells (after transfusion) in millions. (All patients have shown a "direct" rise.) Full line: Average for 34 patients not transfused. Dotted line: Extrapolation line.

From theoretical considerations, transfusion should not be expected to exert any influence upon the rate of regeneration. As mentioned, patients given the purée diet reach the same temporary or final level at the same time. If the lowest blood value is heightened by means of a transfusion, the patients start from a higher level but this would not mean a more speedy regeneration as long as the blood transfused does not live any longer than the patient's own blood. And for this there seems to be no evidence.

Hemorrhage From Other Diseases than Peptic Ulcer. Ten patients having had melena or hematemesis from other causes than peptic ulcer have been tabulated in Table 4 and Figure 5.

These patients all show a definite failure in reaching standard values. Some of the patients are not quite comparable to our ulcer patients, especially those with cancer who are of an age where we

have very little material for comparison (above 60). The erythrocyte rises for the 10 patients have been inserted in Figure 5. All these patients, too, have been given purée diet. No. 59 was given a transfusion.

TABLE 4.—PATIENTS WITH HEMORRHAGE FROM OTHER DISEASES THAN PEPTIC ULCER.

Disease.	Pt. No.	Sex.	Age.	Min. val.	Daily rise.	Deviation from stand.	Day Fe.
Cancer of stomach	55	F	63	1.62	56	-32	
Cancer of stomach	56	F	58	2.99	31	-15	
Cancer of stomach	57	F	70	2.28	44	-24	3
Cancer of colon	58	F	73	2.09	46	-28	
Cirrhosis	59	M	50	0.92	89	(-21)	5
Cirrhosis	60	M	55	1.3	52	(-46)	
Cirrhosis	61	F	68	3.41	24	-10	1
Cardiac cirrhosis	62	F	49	2.25	36	-33	4
Banti's disease	63	F	29	2.91	23	-26	5
Banti's disease	64	M	78	3.43	21	-12	

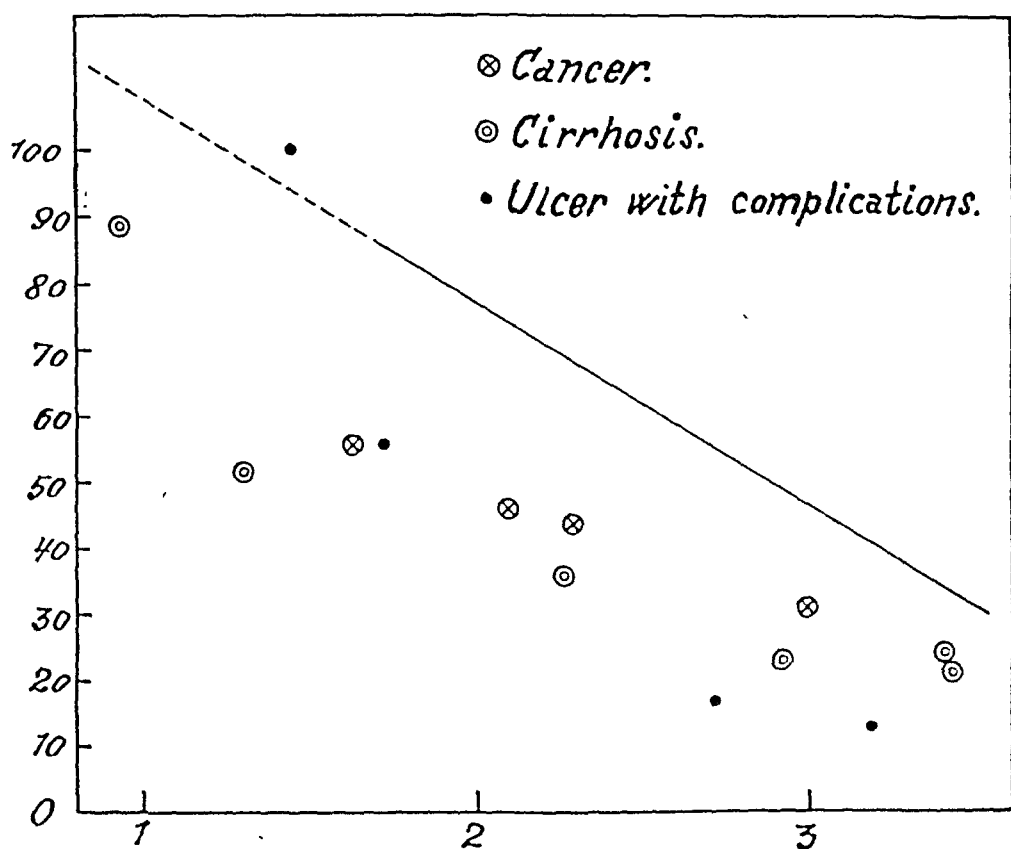


FIG. 5.—Rise in patients with cancer, cirrhosis of the liver or peptic ulcer with complications. Ordinate: daily rise in red blood cells. Abscissa: lowest value in millions. Full and dotted line as in Fig. 4.

Complications. Four patients who were given the same treatment as our standard patients and who like them had a hemorrhage from a peptic ulcer have suffered from some complicating disease. (Table 5 and Fig. 5). No. 67 was given a transfusion.

TABLE 5.—PATIENTS WITH PEPTIC ULCER AND COMPLICATION.

Complication.	Pt. No.	Sex.	Age.	Min. val.	Daily rise.	Deviation from stand.	Day Fe.
Phlebitis	65	F	43	1.44	100	(+ 6)	1
Achylia, tertiary lues . .	66	M	53	1.71	56	-29	3
Undulant fever	67	F	45	2.72	17	-37	
Coli-pyuria, cholelith. .	68	F	67	3.19	13	-27	1

It will be seen that most of the patients with complications show a definite lag in regeneration. The complication in most cases has been some febrile disease. In the patient with achylia it is debatable whether he really has had an ulcer; cirrhosis or cancer seems to us more probable.

Two patients have had a complication of another sort: a constant bleeding from another source than the digestive tract. One, a woman of 40, had a chronic vaginal bleeding; the other, a woman of 55, a hemorrhagic nephritis with considerable loss of blood. Both these patients had a constant fall in erythrocytes during the observation time.

One patient, a man, aged 70, had a melena 1 month and another melena 14 days before admission and hematemesis and melena 2 days before admission. He rose from 1.82 to 3.29 million in 20 days, thus having a daily rise of 74,000, only 9000 below the standard. This shows that even an old man after severe bleeding can rebuild his blood quite well when once the hemorrhage stops.

Conclusions and Summary. We think to have demonstrated that our method for computing the regeneration rate and establishing a standard can be useful when such factors as age, sex, form of hemorrhage, treatment and complications are to be investigated. The results are not very far from what might be expected; still, we find it quite remarkable that neither age nor sex, nor manner of bleeding seem to be of any great importance. Blood transfusion can alter the blood level immediately but has not been able to hasten regeneration. The superiority of the Meulengracht treatment in rebuilding blood in these patients once more has been established. Complications of different sorts show a retarding influence.

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THE INTERRELATION OF VARIOUS SYSTEMIC HEMATOPOIETIC PROCESSES.*

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If one traces the historical development of various branches of the biologic sciences one is impressed by the fact that many of them have followed a strikingly similar course in their method of progress. This consists first of an often long period given over to separation, identification and classification, with a great deal of stress put upon the recognition of specific entities. This is followed by a more recent period in which the interrelation of the previously separated entities is more fully appreciated and studied. To mention several examples, in the inorganic world chemistry busied itself with the discovery of new elements until sufficient were found to lead to their orderly arrangement in Mendeléeff's periodic system and now the gradual transposition of one into another is a recognized fact. On the other hand, in the organic world bacteriology has been concerned with the identification of new organisms, which were held to be quite distinct, but now the intimate relation and even probable interchange of many forms are appreciated.

In the fields of pathology there are many striking examples of this same interesting fact. From the introduction of cellular pathology by Virchow to recent times the literature has been filled with articles dealing with the separation and identification of different disease processes. Nosology controlled the picture. Tumors have been divided and subdivided with most detailed classification. This is important from the didactic standpoint, but one soon comes to realize these are but terms; no sharp divisions exist in Nature. We have overemphasized the precise pigeon-holing of these various growths. Similarly for teaching it is essential to define various types of inflammatory processes which come to stand out as entities, though as a matter of fact they are merely different combinations of simple fundamental biologic tissue reactions and hence cannot be sharply separated one from the other.

No better example of this trend can be found than in the systemic hematopoietic diseases. Hodgkin,¹⁰ of Guy's Hospital, in 1832, published a paper entitled "On Some Morbid Appearances of the Absorbent Glands and Spleen" and thereby called attention to a group of diseases, the separation of which was to occupy pathologists for a century. Virchow,²⁰ in 1845, identified the leukoses:

* Presented in somewhat abbreviated form before the Osher Reporting Society, Montreal, January, 1936.

Cohnheim,² in 1865, described the aleukemic form of lymphosis* which he designated pseudoleukemia; Kundrat,¹² in 1893, separated off the lymphosarcomatoses; Paltauf,¹⁶ in 1897, made a detailed study of lymphogranulomatosis; Sternberg¹⁹ gave the name of leukosarcomatosis to a particular type and the forms with greenish pigmentation of the tissues were recognized. Then subdivision of the main groups arose, as in Ghon and Rhoman's⁹ classification of the various forms of lymphosarcomatosis. As rarer cases were studied many so-called "atypical" types were introduced, and even occasionally very unusual new groups were added, as the case of myelosarcomatosis which we had an opportunity to report.

There arose therefore a detail of classification and nomenclature which was quite beyond the grasp of those not particularly interested in this problem. Clinicians found only confusion and no practical usefulness in the fine distinctions and it was quite in order that a reaction should sooner or later come. It did with the publication, in 1926, by Minot and Isaacs,¹⁴ of Boston, of a paper entitled "Lymphoblastoma" in which they recommended grouping the whole series of systemic lymphoid processes including lymphogranulomatosis, lymphosis and lymphosarcomatosis under this term. Their suggestion met with a most favorable reception and use of the term has become quite popular among physicians. This step was very similar to the introduction by the American College of Surgeons of the term "osteogenic sarcoma" to designate a clinical entity which however was composed of various types of bone tumors having quite diversified histologic characteristics.

Pathologists, as a rule, have opposed this use of the term lymphoblastoma. Ewing,⁶ in discussing the matter a year later before the American Association of Pathologists and Bacteriologists, expressed himself as follows: "Although we may not be able to find clear differences in all cases, how are we going to make progress by throwing them all into one category? I would rather see the most minute differences emphasized and a classification based upon them until the time when the etiologic factors unify or divide the entire group." Recently Krumbhaar,¹¹ in reviewing the subject before the combined meeting of the American and Canadian Medical Associations at Atlantic City, raised objections to its use. He pointed out it implies from its etymologic structure a neoplasm of immature lymphoid cells, but is employed to designate a whole group of conditions many of which by all our criteria are not neoplastic. He introduced instead, though rather apologetically, the less committal term "lymphomatoid diseases," which would merely

* For sometime we have used the term "lymphosis" synonymously with "lymphatic leukemia" as employed by many clinicians and "lymphadenosis" as used by many pathologists. It thus becomes comparable on the lymphoid side to myelosis on the myeloid side. One thus avoids such paradoxical phrases as aleukemic leukemia or the use of a term as lymphadenosis which implies a disease of lymph glands for what is rather a process affecting the lymphoid system.

signify that they simulate tumors of lymphoid tissue. From the pathologic standpoint this name is certainly preferable, but it is not as handy and it is doubtful if it will come into common use.

Now if you were to ask our brief and candid opinion of this whole situation, we should be inclined to answer—the clinicians have called our bluff. We have ferreted out the most detailed differences in these conditions, we have classified and subclassified them and arranged them in a most complete sequence, but we have failed to emphasize the point, which is strikingly obvious at the bedside, namely, that they constitute a series of *interrelated* processes. The sharp separation of these diseases during the past hundred years has been the natural scientific development of the subject; the work was necessary, but it is time to reap the harvest. How may this be done?

There are two possible methods of approach to the problem, of which, however, unfortunately only one is available to us. If we but knew the cause of these conditions it would probably be quite simple to demonstrate their interrelation from the etiologic standpoint. However, our knowledge here is more than grossly inadequate, it is practically negligible. The other method depends upon an analysis of the histologic processes involved in the development of the various pathologic lesions. In other words, we must show that these diseases differ only in modifications of a general proliferative reaction. The weight is thus shifted to the other foot, for we no longer emphasize the differences, but lay stress upon the similarities.

Before elaborating on this method of approach, it might be advisable to review the genetic relationship of the various cells met with in these processes. It is most important to have this clearly in mind, for on it depends a proper conception of the pathologic lesions themselves.

The hematopoietic system is simply that part of the much more extensive reticulo-endothelial system which is concerned with the production of the morphologic elements of the blood. It has two great subdivisions, the lymphoid and myeloid tissues which in extra-uterine life are met with principally in the three main organic entities—the lymph nodes, spleen and bone marrow. In the embryo and under pathologic conditions a much greater part of the reticulo-endothelial system may be given over to this blood cell forming activity.

Throughout the whole reticulo-endothelial system, but most obviously in all the organic entities mentioned above, we meet as the fundamental and primordial root cell, a relatively undifferentiated and highly potential mesenchymal element known as the reticular syncytial cell. These cells are quite large branching elements with pale staining vesicular oval nuclei. Their processes fuse into a loosely arranged network and they lie in intimate relation

to argyrophilic reticular fibers. As stated, they are highly potential, for from them may be derived not only all the various morphologic elements of the blood, but also the specific cells of reticulo-endothelium and the fibrous connective-tissue series. They are not phagocytic.

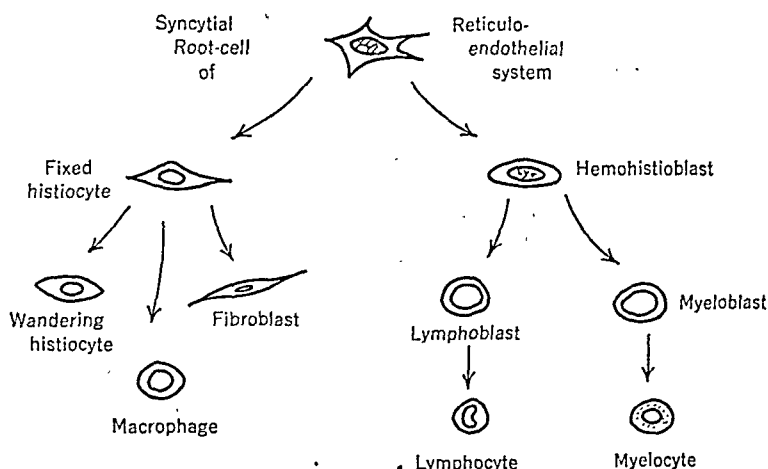


CHART 1.—Diagram of the genetic relationship of the principal elements of the reticulo-endothelial system.

In forming the blood elements there seems good reason to believe, though the arguments for this cannot be gone into here, that these syncytial cells first differentiate into a large common primordial blood cell. This cell retains the ability to form either lymphoid or myeloid elements but loses the other potentialities and, as it never leaves the tissues to appear in the blood stream, is best designated a *hemohistioblast*.* From it may arise either the lymphoblast or root cells of the lymphoid elements or the myeloblast of the myeloid tissues. On the other hand, from our syncytial root cells of the reticulo-endothelial system we obtain the highly phagocytic histiocytes which are so conspicuous in the lymph nodes, bone marrow and spleen and which as littoral cells line the sinuses of these organs. These cells are fixed but from them are derived the wandering histiocytes and large macrophages, which play such an important rôle in inflammatory reactions. These cells probably do not retain hematopoietic potentialities, but can develop into the various elements of the fibrous connective-tissue series. It is obvious, therefore, that we have present throughout the whole reticulo-endothelial system in these syncytial root cells elements which can quite readily

* The term is used in a slightly different sense than by Ferrata who first introduced it. This conception of a common blood cell which differs from the primordial reticular mesenchyme but never enters the circulation and is essentially a tissue element may be designated as histoid unitarism.

under proper stimulations differentiate into a great variety of higher forms.

Now that we have reviewed the vast potentialities of this system, let us consider for a moment the character of the tissue change which may take place. Nearly all of the various systemic hematopoietic diseases are concerned with cell multiplication, that is, they are proliferative in type. For years it has been customary in pathology to recognize two main types of this activity: one consists in the formation of new elements similar to the tissue from which they are derived and having normal functional activity. Such newly formed cells are always under complete environmental control and hence their multiplication is limited. This process is referred to as *hyperplasia*. The second type of activity consists in the repeated formation of cells, which are more or less atypical, fail to reach complete differentiation and retain, if any, only abnormal and perverted functional activity. These cells have apparently lost the normal environmental restraint to growth and hence appear to have assumed a certain independence. This is referred to as *neoplasia*, or tumor growth.

In our earlier studies on the hematopoietic system it became quite clear to us that the gap between these two types of activity was too great to form an orderly sequence and that we must introduce a third form between them, for which we have used the term *kataplasia*. In this form which approaches hyperplasia on the one hand and neoplasia on the other, the cells do not reach complete differentiation and often show certain atypical features of development, but they still exhibit evidence of environmental control and lack the apparent independence of true neoplasms.

The introduction of this intermediate type of activity has been a great help in interpreting and teaching the interrelation of the various hematopoietic processes, but imagine our delight when on applying the same idea to other parts of the body it became obvious that it was not merely a convenient term, but seemed to express a fundamental principle of the proliferation of cells under pathologic conditions. To mention an example, one finds in tracing the development of cancer of the breast from the simple epithelial hyperplasias an intermediate stage in which the cells lack complete differentiation and appear atypical but as yet are not emancipated and never at this stage exhibit metastases.

We do not mean to imply by bringing up the distinction between these various types of proliferative activity and arranging them in a sequence, that in all cases of tumor growth one can readily distinguish the three steps. Transformations of hyperplasias into neoplasms undoubtedly occur without at least any apparent introduction of the kataplastic phase. However, it is quite possible that under such circumstances the steps are taken too rapidly to be readily recognized.

To recapitulate, therefore, we may say that we have in the hematopoietic organs a system of cells, headed by the highly potential syncytial reticular elements, which may under abnormal stimulation undergo a series of interrelated proliferative activities which vary all the way from simple hyperplasia, through kataplasias, to true neoplastic growths. Because of the diversified potentialities and the various grades of activity the possible end results as we see them in the patient are almost infinite. Some of them are doubtless more common than others and these have been identified and given various names as entities by different observers, but no sharp separation actually exists in Nature; our classification is purely arbitrary.

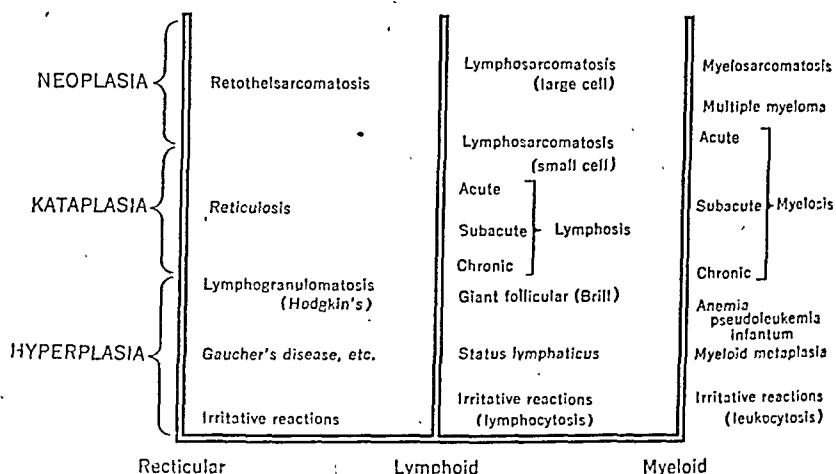


CHART 2.—Diagram of the interrelationship of various diseases of the reticulo-endothelial system.

Should we desire for didactic purposes to chart the interrelation of these processes with the well-recognized disease entities, we might do so as follows: We erect three tall columns representing the three main forms of the proliferative activity of the reticulo-endothelial system, first the myeloid, second the lymphoid and third the reticular form. At the bottom of these we place the hyperplasias, above them the kataplasias and at the top the neoplasias.

In the myeloid column as we ascend we meet first the marked myeloid hyperplasia, associated with long-continued leukocytosis, as in chronic sepsis. This reaches an extreme degree bordering on kataplasia in the *anemia pseudoleukemia infantum* of von Jaksch. We then in ascending to the kataplasias enter the more chronic forms of myelosis, which grade all the way up through the subacute to the acute sarcoïd types, having many features of true tumors, while at the top rest the multiple myelomata and myelosarcomatosis.

In the lymphoid column we first have simple hyperplasias which are met in many irritative processes and which reach a higher degree in status lymphaticus and the giant follicular hyperplasia of Brill. We then encounter among the kataplasias the chronic lymphosis of adults, the subacute form of childhood and then the acute form only met with in infancy. Above this we pass into the lymphosarcomatosis of Kundrat.

And in the third column of reticular activity we place among the hyperplasias at the base, first the simple irritative hyperplasias and those associated with the highly phagocytic storing capacity of the cells as expressed in Gaucher's disease and similar conditions.

Above these and approaching the kataplasia because of the abnormal and often atypical features of the hyperplastic activity comes Hodgkin's disease, or lymphogranulomatosis. With it are often certain exudative features and the laying down of abundant collagenous fibers. Corresponding to the leukoses of the lymphoid and myeloid series we have here the rare and only recently described reticuloses, and finally in the neoplasms the true reticular-cell tumors, or retiothelsarcomatoses.*

It is interesting to note that in lymphogranulomatosis we quite frequently have an ascending of the scale into a neoplastic process known as Hodgkin's sarcoma. It is a tumor of the reticular elements.

This is a convenient chart for didactic purposes, but its principal value is that it impresses upon us the artificial character of our divisions into entities and the interrelationship of the whole. With it the interpretation of atypical and so-called intermediate cases becomes comparatively simple, at least we rest in the assurance that we have a reasonable explanation for their occurrence.

For example, we recently observed a case having all the gross pathologic features of lymphosarcomatosis but with a leukemic blood picture. Histologic examination revealed a form of proliferative activity lying between the kataplastic lymphosis and neoplasia. This approach to the kataplasias evidently allowed for entrance of the cells into the blood stream. Such a case is hard to classify, but simple to understand.

Another phenomenon which it has helped us to interpret is the fact that acute myelosis is so much more common than acute lymphosis, while myelosarcomatosis is much rarer than the corresponding lymphosarcomatosis. If we apply the principle of interrelationship it seems quite certain it is because the lymphoid cells cease to enter the blood stream at a much lower point in the column

* In our discussion of the cytogenesis of the blood elements we have purposely avoided introducing the monocytes as a separate line of blood-cell development. While we quite appreciate there are many points favoring the triallistic view from the experimental fields, this is not supported in our experience by the hematopoietic diseases as they appear in man. We have as yet to see a so-called "monocytic leukemia" which on careful study and following of the case did not prove eventually to be a myelosis.

than the myeloid cells and consequently we assign to the lymphosarcomatosis a larger portion of the lymphoid column, while the corresponding myeloid area comes under the myeloses.

Another problem which has always been the subject of a great deal of argument in pathology seems to be quite readily explained by this conception. For years lymphogranulomatosis has been looked upon as an inflammatory process while lymphosarcomatosis was neoplastic, still there appeared to exist intermediate types between the two conditions. The confusion has been due to the impossibility of defining the limits of what one considers inflammatory. After all, the predominating features of Hodgkin's disease are proliferative and the high potentiality of the reticulo-endothelial tissues can explain the great variety of histological pictures which occur in this condition, even to the formation of the collagenous fibers. If there are certain exudative features it does not alter the fact that the process is primarily the result of certain biologic influences which stimulate the cells to proliferation and which as in all these diseases are brought to bear on the reticulo-endothelial tissues.

It is interesting to note that there is a great deal of support for the idea of the interrelationship of these diseases from the experimental fields. Fisher-Wasels⁷ and his co-workers have been able to produce, in animals treated over a long period with tar, by the injection of indol, various types of reaction which in some cases take the form of lymphosarcomatosis, in others either lymphoid or myeloid leukemias. Also Furth,⁸ at Cornell, has caused the development in chickens of a great variety of reticulo-endothelial reactions by means of a single filterable reagent. These vary all the way from hyperplastic processes to what he is satisfied to consider tumors. That is, it has been shown experimentally that the same etiologic factor can produce reactions in the reticulo-endothelial system which fall into different entities of our classification. This is a very convincing corroboration of our views and a death blow to any conception based on the specificity of each condition.

To our minds it is quite as ridiculous to draw a sharp line between many of these hematopoietic diseases as it is to separate clearly the various histoid tumor growths ranging from the highly differentiated fibromas down to the very immature spindle-cell sarcomas. Such divisions are arbitrary, and only a convenience for purposes of classification, record and teaching. They do not exist in Nature. At the same time no one would recommend giving them up. They serve a very distinct and useful purpose with this limitation.

To the clinician they should remain as diagnostic disease entities, but he should ever bear in mind that transition types may readily occur and consequently a sharp separation may frequently be quite impossible. On the other hand, the pathologist, and more particularly he who is responsible for the diagnosis of biopsy material, should find the concept outlined here very useful. There is a distinct

difference in approaching a slide of enlarged lymph gland, for instance, with the idea of placing its lesion at once in one of the well-recognized hematopoietic diseases, from first analyzing the nature and character of the proliferative changes which have taken place and determining the position which it occupies in a series of closely related processes.

Summary. Our identification and separation of the various disease processes of the hematopoietic organs which are characterized by proliferative activity have reached a stage where it is advantageous to take cognizance of their interrelationships. This may be done by consideration first of the genetic relationship of the various cells of the reticulo-endothelial system, and second, the types of proliferative activity which they undergo. On this basis these various diseases form a quite definite series which blend from one into another. Moreover, by such a conception the interpretation of many so-called atypical forms becomes comparatively simple and intelligible.

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PHYSIOLOGIC AND SYMPTOMATIC EXPECTANCY FOLLOWING SUBTOTAL GASTRECTOMY.

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DURING the past few years it has been the opportunity of one of us (E.S.T.) to manage medically a number of patients who at some previous date have been subjected to a subtotal gastrectomy. The

literature on the postoperative results attending this type of surgery is not meager. However, a goodly portion of it is relative to isolated physiological phases of gastric function rather than to the clinical status of the patient at varying postoperative periods.

Two questions seemed to us of importance in a postsurgical study of partially gastrectomized patients. First, are there enough after results of gastric resection, common to all cases, to allow the physician to anticipate to his patient what he may expect as the result of surgery? Second, may any phase of the patient's preoperative condition particularize to that individual what his postoperative state is most likely to be?

In an endeavor to answer these questions, we have studied an admittedly small series of 26 partially gastrectomized patients. This survey included a stool analysis, study of the gastric secretory function, the hematology of the patient, a Roentgen ray study of the stomach, and careful interval history since the date of operation.

In this group of 26 patients, 16 were operated upon for duodenal ulcer and 10 for gastric ulcer. Table 1 gives the comparative time since operation, sex, and age at the time of the present analysis. The longest period of time since operation was 12 years; the shortest was 5 months.

TABLE 1.

Males	17
Females	9
Operation less than 1 year	6
Operation between 1 and 5 years	11
Operation over 5 years ago	9
Age at time of present analysis:	
30 to 40	7
40 to 50	6
50 to 60	6
60 to 70	5
70 to 80	2

All the cases were operated upon by one surgeon, and according to the technique of Richter.²⁰ This operation has its origin in the second operation of Billroth and consists of a wide resection of the stomach including especially the lesser curvature and magenstrasse, with an end-to-side gastrojejunal anastomosis. The lesser curvature border is closed partly to make a spur which tends to prevent the passage of stomach contents in the wrong direction (Fig. 1).

In short, the operation is a subtotal removal of the lesser curvature and distal half or more of the stomach, spur formation at the lesser curvature and a vertical position of the stoma in the standing position of the patient. This leaves approximately 40% of the fundus.

From a physiologic standpoint, gastric secretion is divided into four separate phases and is not a single response to the stimulus of food intake. The primary or cephalic phase is initiated by seeing, tasting, smelling and swallowing food, starting almost immediately

and lasting about 15 to 30 minutes.¹⁸ The mechanism of stimulation is probably through the vagus nerve. The secondary phase is initiated when food chemically stimulating the pylorus of the stomach causes the fundus, wherein the gastric glands are located, to secrete. According to Ivy⁶ this phase is hormonal or secretagogue in type, as isolated fundic pouches in dogs, where an extrinsic nervous mechanism cannot be associated, will secrete upon chemical or mechanical stimulation of the antrum with food. Klein and Arnheim¹¹ report similar results. Priestly,¹⁹ however, feels that the removal of the antral phase in dogs, at least, does not effect the concentration of gastric secretion from the gland-bearing fundus. The third phase is intestinal, appearing late, probably 1 to 6 hours after food intake.⁸ Very little is known about this phase of gastric secretion. The fourth factor is the spontaneous or continued secretion, varying in amount from 2 to 50 cc. and independent of food intake.¹

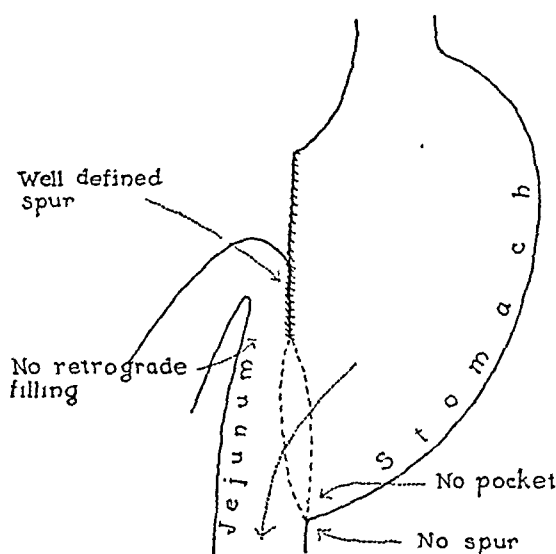


FIG. 1.—Richter: Diagram of Surgical Procedure. (Courtesy of Surg., Gynec. and Obst.).

A considerable amount of statistical data has been published concerning the influence of resection of the antrum of the stomach upon the secretion of hydrochloric acid in both duodenal and gastric ulcers. Klein^{10b}, in a series of over 100 cases of partially gastrectomized patients, found a wide variation in the acid secretion, ranging from complete achylia gastrica to hypersecretion. He concluded that in removing only one phase of secretion, namely the antral one, and leaving the three other factors concerned, the end result depended entirely upon what per cent of the total secretion the antral phase played. This is undoubtedly an individual variable. Patients whose pre-operative gastric secretion was due in a large percentage to the antral phase consequently would tend to have a lower post-

operative acidity if that factor was removed. Another factor he concluded is the reflux of neutralizing substances into the stomach, namely pancreatic juice and bile. Even the test meal and saliva tend to neutralize the existing free hydrochloric acid. Their achlorhydria patients were found to occur more frequently in those cases operated upon for gastric ulcer than for duodenal ulcer, explained in part probably by the fact that inhibitory impulses to gastric secretion originate in the early duodenum,¹³ and possibly removal of these inhibitions tend to permit greater secretion. Comfort and Osterberg¹ found only 20% of their partially gastrectomized patients to have an achlorhydria, using, however, histamine and not a test meal as a diagnostic means. According to their interpretation, since Priestly¹⁹ showed that the removal of the antral portion of the stomach in dogs did not influence the concentration of free acid obtained from the fundus, and that the antral mucosa apparently did not play an essential part in the formation of a hormone necessary to the chemical phase of secretion, there was therefore no reason why the cells should not secrete as well postoperatively as before operation. Shapiro and Berg,²³ after a subtotal gastrectomy and double vagotomy in dogs, induced only a temporary reduction in gastric secretion (acidity) which was followed by a return of acidity and secretory function. Lorenz and Schur¹⁴ reported 75% of their patients with subtotal gastrectomy to have an achlorhydria. Lewisohn,¹² in 1927, reported 77% anacidity after operation. Klein^{10a} concluded that an immediate hypoacidity and achlorhydria in 78% of cases operated upon for gastric ulcer and 18% for duodenal ulcer occurred and that these percentages rose to 100% and 66% respectively after 6 months.

Gastric Secretion. Our method of secretory analysis consisted in passing a Rehfuess tube into the stomach, and then retracting it just beyond the sphincter action of the cardia whereupon air could be aspirated from the esophagus. The tube was then again lowered not over 3 to 5 cc. into the fundus of the stomach. This procedure we feel could not have allowed the tip of the tube to lie in the jejunum. A fasting specimen and 15-minute specimens of gastric juice for 2½ hours were removed from the stomach, after a test meal consisting of two slices of bread and 400 cc. of water was given. One patient received 80 cc. of 7½% alcohol in place of the bread and water meal. All gastric analyses were taken in the morning and upon an empty stomach. Eight achlorhydria patients were given 0.5 mg. of histamine hypodermatically after they failed to show free acid with the above-mentioned meal (Table 2).

TABLE 2.

Number of patients with free acid	9
Number of patients with an achlorhydria	17
Number of patients given histamine	8
Number of patients showing acid after histamine	3
Number of patients having bile in fasting or first specimen	12

As may be noted, 17 of the 26 cases of partial gastrectomy in our series (65%) had an achlorhydria with our technique of investigation, leaving 9 cases (35%) with working free hydrochloric acid. By working free hydrochloric acid is meant enough acid present to be expressed in a measured degree with Töpfer's reagent when titrated against N/10 sodium hydroxid solution. The combined acid was not interpreted as a measure of the degree of the secretion of hydrochloric acid, as in none of our cases did we find a combined acidity of over 8° when free acid was not demonstrable. Neckeles and Scheman,¹⁷ using continuous aspiration and titration of successively minute amounts of gastric secretion, found some free acid in very small amounts in 18 of 20 patients with partial gastrectomy. However, such small amounts are inadequate for normal digestion at least from a clinical standpoint, and may be explained in part on the basis of the spontaneous or continuous secretion.¹

Of the patients with measurable amounts of free hydrochloric acid, 5 had free acid of less than 5° in all specimens, the remaining 4 having a higher range between 10 and 50°. We have purposely not included those patients showing free hydrochloric acid only after histamine stimulation, because we feel as do many others, that the secretion following histamine is not a normal secretory response as is the response to food intake. There are three reasons for this viewpoint. First, histamine is a powerful chemical stimulus of the gastric glands themselves. Second, the other three above mentioned phases of gastric secretion are not included. Third, the nature of the secretion is in a pure state, undiluted with test meal or saliva. However, 8 patients presenting an achlorhydria were given histamine and 3 were found to have free acid after the injection. This left us with the supposition that the remaining 5 patients were absolute achlorhydric cases.

The question of the neutralization of gastric secretion by the reflux of pancreatic secretion and bile is frequently considered as a factor in the production of, or rather the interpretation of, an achlorhydria. It has been stated that the value of histamine in the study of chemical values after partial gastrectomy, lies in disclosing free acid masked by the neutralizing influence of the base in the regurgitated duodenal or jejunal contents.³ That, at least in our patients, the reflux of bile is not uncommon, can be concluded from the fact that 12 of the patients in our series had a trace of bile in either the fasting specimen or first 15-minute specimen after the meal or both. Only 2 patients having bile in their fasting or first specimen were found later to have a measurable amount of free acid. In the 7 remaining cases of the original 9 having free acid, no bile was found at any time.

Seven of the 9 cases having postoperative free acid (77%) had been operated upon for a duodenal ulcer. This is in accord with the findings of Klein, namely that duodenal lesions are more apt to

have an adequate amount of free acid after operation than are those patients operated upon for gastric ulcers.^{10b} An effort was made to correlate the incidence of a continued high postoperative curve with a high preoperative curve.⁴ Of 8 cases with free acid before operation of over 50°, only 4 had postoperative acid at all, and of these, the highest degree of free acidity was 32°. Thus we concluded that a high pre-operative curve does not necessarily mean that the patient will have a high postoperative curve, and in reality he has, at least in our small series, a 50% chance of having an anacidity.

Postoperative Anemia. The question of the occurrence of an anemia following subtotal gastrectomy and its interpretation is, as yet, only partly understood. Castle, Townsend, and Heath² postulate that an intrinsic factor is necessary for the development of a substance which causes red blood cells to mature, and that this substance is present in the gastric juice obtained from apparently normal individuals, but not found in the gastric juice of patients with pernicious anemia and achlorhydria. Meulengracht¹⁵ proved that in the pig, at least, the pyloric glands and Brunner's glands in the duodenum were the productive sites of Castle's intrinsic factor, the fundal glands being inert from this standpoint and the glands of the cardia still open to question. Unless the intrinsic factor exists at least in part in the human duodenum, one might well suspect that the subtotally gastrectomized patient was being deprived of the necessary antanemic factors and that some form of anemia should be found in these patients.

Ivy, Morgan and Farrell⁹ suggested, after observing partially gastrectomized dogs up to 10 years after operation, that the factor of safety in the digestion of protein and iron was reduced, because all their female dogs developed a secondary or hypochromic anemia when the added strain of pregnancy was imposed, apparently responding, however, immediately to subcutaneous iron without a change in diet. Rosenthal and Abel²² found in a series of 114 cases of subtotal or total gastrectomy, no cases of pernicious anemia; however, 14% had a varying degree of secondary anemia. Walton²⁴ found only 6 instances of secondary anemia in 794 cases.

In an effort to determine what the blood pictures were in our group of 26 cases, each was subjected to a complete blood count and smear, hemoglobin determination with a Sahli hemoglobinometer and hematocrit reading. Only 1 patient had a count under 4,000,000 red blood cells, this being 3,850,000 with 10.2 gm. of hemoglobin, and was interpreted as a mild hypochromic anemia. All hemoglobin determinations expressed in grams were normal, although 5 patients had low normal values between 13.5 and 14 gm. for red blood counts of 4.5 million cells. Hematocrit interpretations were normal and varied between 4 and 5.3. These findings taken collectively would suggest that at least sufficient intrinsic factor was being produced, possibly as suggested by Meulengracht,¹⁵ from

Brunner's glands in the duodenum, as the pylorus in all cases was absent. In addition they would suggest and in accord with more recent views, that gastric resection in man is more likely to be followed by a hypochromic or secondary anemia than by pernicious anemia, and that when pernicious anemia does occur after gastrectomy, it is probably an accidental happening.⁹

Dilatation and Emptying Time. No reference could be found in the literature relative to the hypertrophy of the remaining fundus in man following partial gastrectomy. Milanes,¹⁶ however, states that there ensues some widening of the gastric stump and anastomotic loop in the postoperative cases he reviewed. Of 12 partially gastrectomized dogs in which approximately 66% of the stomach was removed, Ivy⁵ found that 9 dogs developed both definite hypertrophy and dilatation of the remaining stomach which was quite evident at 2 months and maximum at 6 months postoperatively.

Each patient of our group was given a Regal motor meal and 200 cc. of a 2-ounce water suspension of barium to be sipped with the meal. The emptying time was noted. The stomach was then filled with barium mixture to determine the approximate size of the remaining fundus, and one Roentgen ray plate taken. Two normal unoperated-upon patients, used as controls, by the same technique were found to have a complete emptying time of between $3\frac{1}{2}$ and 4 hours.

In our series, 20 patients (77%) had a complete emptying time of the stomach of $2\frac{1}{4}$ hours or less. Four of these emptied so rapidly that by the time they had finished their meal and entered the fluoroscopic room their stomachs were almost empty. In the remaining group of 6 patients having an emptying time of over $2\frac{1}{4}$ hours, all were empty of the opaque barium at $3\frac{1}{2}$ hours, but a high fluid level was still present indicating that these stomachs were really not empty. Undoubtedly some food was still mixed with this fluid and the barium had merely settled out and passed on into the small bowel. We were unable to determine the cause of this delay in emptying time, whether due to a small postoperative stenosing stoma, or to a sphincter action of the jejunum could not be determined. However, it is interesting that of these 6 patients retaining fluid after $3\frac{1}{2}$ hours, all were without symptoms related to this relatively increased emptying time. While some of the stomachs varied quite notably in size, no positive Roentgen ray evidence of dilatation could be set forth. Neither could we observe any definite jejunal dilatation.

Recurrent Ulcer. In all gastric surgery for peptic ulcer, the question of recurrence of ulcer, both marginal and small bowel, is imminent. Ivy and Fauley⁷ found the duodenal mucosa more resistant or less sensitive to acid gastric contents than the jejunal mucosa. Rienhoff²¹ states that in gastrojejunostomy, jejunal

ulcers occurred in 25% of the cases. Of 12 partially gastrectomized dogs, Ivy⁵ found 3 had developed jejunal ulcers.

In our series of 26 patients, 2 cases of postoperative jejunal or marginal ulcer were noted. One had definite Roentgen ray evidence of the lesion just below the surgical stoma and the other had had three separate hemorrhages since operation 10 years before, which we took as evidence of an existing lesion. Neither case gave a symptomatic picture of ulcer. In this relatively small series of cases it is impossible to state definitely that a gastrojejunal ulcer is more likely to occur in a patient having a continued free acid secretion after operation, than in one having an achlorhydria, but it is worthy of mention that both of the recurrent postoperative ulcers in our group were observed in patients who had between 10 and 30° of free acid in all specimens.

Small and Large Bowel Status. It is a well known fact that one of the most common causes of a chronic diarrhea aside from those of bacterial or protozoal origin is an achlorhydria. It is to be remarked that with the production of an anacidity in such a large percentage of cases following partial gastrectomy and with a fairly high grade hypoacidity in others, especially when associated with a stomach which empties considerably more rapidly than normally, one would expect a goodly proportion of these cases to develop a mechanically irritable bowel. All patients in our series were maintaining themselves on a general diet, save one who was excluding only meat. Eight patients gave a history of having from 2 to 10 "attacks" yearly of semiformal to loose stools, associated either with abdominal cramps, abdominal soreness or flatulence. Only 1 patient in this group of 8 had available free hydrochloric acid. All had been operated upon over 3 years prior to the time of this examination, save 1 whose operation had been 8 months previously. It is worthy of mention that in our series of patients, 9 were females and 5 of these were in the group of 8 complaining of an irritable bowel syndrome. One was severe enough to present a definite nutritional problem, passing bulky undigested food in her stools. In addition to these 8 cases above mentioned, 7 voluntarily stated that a definite increase was noted in flatulence over what they had experienced pre-operatively. Thus a total of 15 cases (58%) of our group complained of some form of intestinal unrest.

General Symptoms. Two patients complained of discomfort in the form of a dull pain or a sensation of pressure in their stomachs if food was eaten relatively rapidly. Two more found that if food was not taken frequently, dizziness or weakness almost approaching syncope occurred. Only 1 complained of water brash.

Thirteen patients (50%) maintained the same weight as prior to operation; 8 (30%) had gained in weight, while 5 (20%) had lost weight. Five (20%) complained of easy fatigability and 7 (27%) stated that they had decidedly less strength than before operation.

Realizing of course that the question of weight and strength are both subject to rather great individual interpretation, we present these averages merely for the interest they may arouse.

Summary. From a clinical, physiological, and symptomatic viewpoint, just what does the future hold for the average patient subjected to a subtotal gastrectomy? Because we were interested in this question we studied the secretory function, hematology, motor function, and postoperative history of a relatively small group of 26 patients.

In 65% of the cases, a postoperative achlorhydria was found. The probability of a patient having working free hydrochloric acid after his operation was greater if he had had a duodenal ulcer than a gastric ulcer. Also because a patient had a high pre-operative acid curve, in our series at least, did not mean that the postoperative acid curve would be high. In fact, in 50% an achlorhydria was found. Only 2 of 12 patients having bile in the fasting or first specimen had free acid in following specimens. Certainly neutralization with alkaline duodenal contents is a factor in some cases.

No gross blood changes were observed. Only 1 patient in 26 had a red blood cell count under four million cells, this being 3,850,000. Five had low normal hemoglobin determinations with normal red blood counts of over four and one-half million cells. All hematocrit readings were within normal range.

The motor emptying time of the stomach was found to be decreased over the normal of $3\frac{1}{2}$ hours in 79% of the cases. Twenty-one per cent still had a high remaining fluid level at $3\frac{1}{2}$ hours. No cause for this difference in emptying time could be determined. However, these patients were asymptomatic. No positive evidence of gastric dilatation or hypertrophy could be determined, although the size of the remaining fundus varied moderately as would be expected.

Fifty-eight per cent of the series gave a history of some form of intestinal unrest, and of 8 cases with a definite irritable colon syndrome only 1 had available free hydrochloric acid.

No patient had a postoperative continuance of the chemical distress of ulcer following operation, although there were 2 instances of ulcer recurrence. All stools were negative for undigested food and blood, save 1 case of diagnosed jejunal ulcer which revealed occult blood in his stools.

Fifty per cent maintained their weight since operation, 30% gained weight, while 20% had lost weight. Forty-three per cent complained of either easy fatigability or less strength.

Conclusions. 1. Sixty-five per cent of our cases had an achlorhydria.

2. A postoperative achlorhydria was more common in gastric ulcer than duodenal ulcer.

3. A high pre-operative acid curve did not necessarily mean a high postoperative acid curve.
4. Reflux of bile is a definite factor in the interpretation or production of an achlorhydria.
5. Only one relative secondary anemia was observed.
6. The emptying time of this type of operated upon stomach is usually decreased.
7. No postoperative dilatation or hypertrophy of the stomach was observed.
8. Fifty-eight per cent of our cases gave a history of some form of intestinal unrest.
9. Two of 26 cases had a recurrent marginal or jejunal ulcer.

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THE TOLERANCE OF CERTAIN CARDIAC PATIENTS FOR VARIOUS RECUMBENT POSITIONS (TREPONNEA).

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CERTAIN cardiac patients who can lie comfortably in one recumbent position, usually the right lateral, cannot tolerate another recumbent position, usually the left lateral, and are forced to

abandon the latter for the former by symptoms which they cannot endure. This phenomenon, which for the sake of brevity we will call "trepopnea,"* is just as common and just as definite as orthopnea. There are certain indications that trepopnea and orthopnea are related, and that both may be manifestations of the same type of underlying mechanism.

The fact that some patients with heart disease do not like to lie on the left side is apparently known to most experienced physicians, with whom we have discussed the problem. We have twice encountered brief statements regarding this fact in the literature.^{5,3} However, we can find no evidence that trepopnea in cardiac patients has ever been the subject of careful study. If it has been, the results of such investigation are not common knowledge. Consequently in this paper, certain observations concerning it are reported.

Cardiac patients of all available types have been studied. They were placed in various recumbent positions and watched. They were not questioned until their appearance and behavior in the different positions had been observed. They were then questioned carefully about the symptoms they had experienced. They next were asked to resume the unfavorable position and to describe each sensation as it appeared and, finally, were requested to move to a favorable position and to describe the disappearance of their symptoms. In addition, certain observations, to be described below, were made with the subjects in the various positions.

On the basis of this type of study, the patients were found to group themselves into four general categories: (1) Those who could lie comfortably in any recumbent position; (2) those who preferred one position, or objected to another for relative minor reasons, such as habit, or annoyance at hearing or feeling the heart beat; (3) those who had more compelling reasons for preferring one recumbent position to another, who experienced dyspnea and discomfort in the chest when in the unfavorable position, but who could endure it; and, finally (4) those who were actually forced to abandon one recumbent position for another by symptoms which they could not endure. The last two groups constitute the material upon which this paper is based. At first only the patients in Group 4 were studied, but it soon became evident that there was no very clear-cut dividing line between the individuals in Group 3 and those in Group 4. Patients in the two groups described the same symptoms and exhibited the same behavior. Those in Group 4 either experienced greater discomfort or possessed less fortitude. It was

* We have been unable to find a term which completely expresses in one word "preference for a certain recumbent position," "objection to a certain recumbent position," or "relief of dyspnea by rotating the body on its horizontal axis, from one recumbent position to another." The term "trepopnea," suggested by Dr. Richard A. Kern, has therefore been applied to this phenomenon. It serves a useful purpose in reducing the number of words in this paper.

not always possible to distinguish between these two possibilities in borderline cases.

Trepopnea is a clear-cut entity, characteristic in its manifestations, both of behavior and complaint. Although it can be readily demonstrated in many patients, information concerning it is rarely volunteered. When present in its advanced form, selection of position becomes a matter of real necessity rather than one of mere preference.

The following observations have been made on 52 patients who showed definite trepopnea, 32 in Group 3 (trepopnea of preference) and 20 in Group 4 (trepopnea of necessity).*

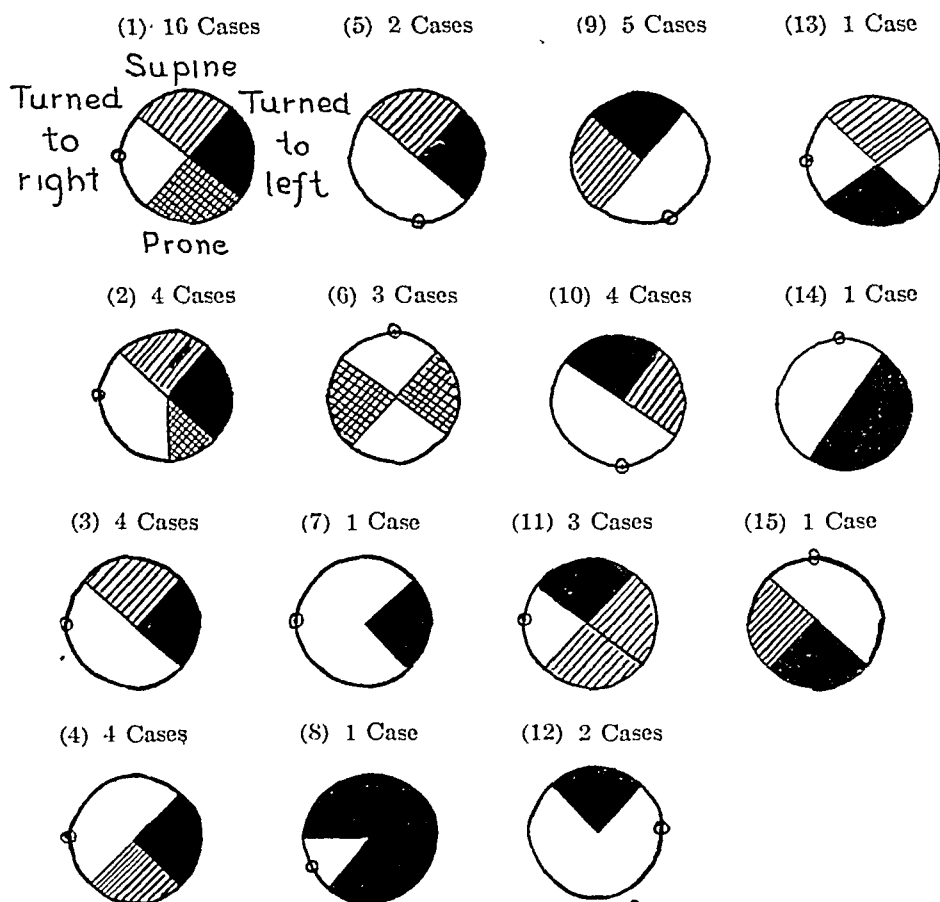
A. Position. Of the 52 patients, 33 were most comfortable lying on the right side; 35 were least comfortable on the left. The prone and supine positions enjoyed an intermediate preference. Chart I constitutes an attempt to indicate the various position-preference patterns. The most common pattern was for the patient to prefer the right side, inclined slightly toward the front or back; to lie prone and supine with moderate discomfort; and to be most uncomfortable turned toward the left. However, there were many variations, 15 to be exact. Some patients can lie prone or on the left and cannot tolerate the supine or the right lateral position. An unexpected type of trepopnea was seen in 9 patients who were most comfortable flat on the abdomen and least comfortable flat on the back (Chart I, (9) and (10)). Some of these patients might well be described as orthopneic, since they were unable to lie on the back unless the head of the bed was elevated 45 degrees; however, they could lie face down without even one pillow. This type of patient when sitting up was comfortable leaning forward and sometimes uncomfortable leaning backward. Many of our patients could lie flat on the right side but needed several pillows to enable them to tolerate the left lateral decubitus. A striking fact was that the dividing line between a comfortable and an uncomfortable position in many patients was very definite. A slight rotation of the body often produced a marked difference in symptoms. The position of the head and neck seemed important in some cases. Flexion of the head on the trunk increased the comfort of many individuals. This was true when the patient was supine but in some cases also occurred in the lateral decubitus. Some patients are impressed with the importance of the position of the arms. A number of individuals have changed or lost completely their trepopnea as will be described below.

Certain cardiac patients in severe congestive failure could not tolerate recumbency in any position for very long, but did have a definite preference for one over another. A few were intolerably dyspneic in all horizontal positions; and had no preference. Both

* These terms have been used previously to describe different degrees of orthopnea.

types were most comfortable sitting up, though not necessarily free from dyspnea. Finally, there were certain individuals with marked congestive phenomena who could lie comfortably in all recumbent positions. Shortness of breath, if present, was not related to posture.

CHART I.—THE VARIOUS POSITION-PREFERENCE PATTERNS OF 52 PATIENTS WITH TREPOPNEA.



Each diagram shows the entire 360 degrees of possible recumbent position as seen by an observer standing at the foot of the patient's bed. The best position is marked with ⊙. The shaded portions of the circle indicate the positions which are not liked. The most deeply shaded is the most unfavorable position. For instance, the individuals depicted by the first diagram in the upper left-hand corner were most comfortable on their right, most uncomfortable on their left, and moderately uncomfortable prone and supine. The 20 cases in Group 4 (trepopnea of necessity) were distributed as follows: (1) 9 cases, (2) 2 cases, (3) 1 case, (4) 2 cases, (9) 4 cases, (10) 1 case, (11) 1 case. In 5 cases in (1) and in both the cases in (12) the degree of discomfort lying prone is not known. In (6) 1 patient was more comfortable on the left than on the right; a second showed the reverse; the third was equally uncomfortable on both sides.

B. Symptoms. The symptoms which forced patients to change from one horizontal position to another were usually dyspnea and discomfort in the region of the heart. Less common manifestations

which compelled them to move were cough and anginal pain. These and other less cogent, but nevertheless characteristic, symptoms will now be taken up in detail. Their relative frequency is shown in Table 1.

TABLE 1.—THE RELATIVE FREQUENCY WITH WHICH THE VARIOUS SYMPTOMS WERE OUTSTANDING COMPLAINTS IN AN UNFAVORABLE RECUMBENT POSITION.

	Group 3, trepopnea of preference.	Group 4, trepopnea of necessity.	Total.
Total number of patients	32	20	52
Dyspnea	30	20	50
Precordial discomfort	22	16	38
Palpitation	7	10	17
Fatigue and weakness	5	6	11
Cough	4	6	10
Angina	2*	1†	3
Nervousness and restlessness	1	2	3
"Heart beating in fingertips"	2	0	2
Dizziness	0	3	3
Epigastric pain	1	1	2
Pain in neck, left shoulder or arms	2	1	3
Fullness in head and feeling of eyes bulging	3	1	4

* Not observed by us.

† Observed by us.

1. **DYSPNEA.** This is often described as "shortness of breath," or as a "smothering feeling." Patients have said "I get all choked up, you can hear it in my voice," or "I can't breathe;" "I feel that something is cutting off my air;" "I have to pull harder to get my wind;" "I feel as though I were breathing against a resistance;" "my air won't go all the way down." Some say they can't breathe so deeply, so they have to breathe more rapidly. Of all the symptoms which force patients to move, this is probably the primary one. When one individual moved back to his favorite position, he said he felt "as though a window had been thrown open in a stuffy room."

2. **DISCOMFORT IN THE REGION OF THE HEART.** This symptom is very closely associated with the sense of choking or smothering just referred to. It is often described as "a heavy feeling;" "a pressing feeling;" "a feeling as though I were trying to squeeze through a door and couldn't quite make it;" "as though something was tightening around my heart." It is sometimes referred to as a "soreness" or a "gnawing" or an "aching feeling," or "as though something were blowing up inside me." One colored man said: "I feels as if all my entrails is falling over there and pressing." The sensation is a constant one, not throbbing or changing in intensity with the heart beat. It is totally different from palpitation or awareness of the heart beat, though it may occur coincidentally with "palpitation." One patient who also had attacks of angina pectoris said it "was not that (*i. e.*, anginal) sort of pain." When

the patient lay on the left, the sensation was usually referred to the region of the apex. When he lay on the back, it often "rose higher in the chest" or became substernal—"as if someone had placed a weight on top of my chest." It was occasionally felt in the left shoulder, in the scapular region or in the neck. These patients often say "I can't lie on my heart, because the pressure hurts." However, when they are only partly on the left side, with no contact between the precordium and bed, they may have the same discomfort. Therefore, some of the "pressure" must be generated within the chest.

3. COUGH. This symptom was often a very compelling one. In several instances it seemed to be a direct outgrowth of the choking sensation described as the first symptom. It was produced in 3 patients by lying on the left, in 6 by lying on the back and in 1 by lying on the right. It was relieved in each case by the assumption of the opposite position.

4. ANGINA. Three patients reported that they sometimes experienced anginal attacks when they lay in the wrong position,¹⁵ 1 when on the back, 1 on the left and 1 on either right or left. We were able actually to observe such an episode only once. In that case, the patient was uncomfortable as a result of symptoms (1) and (2) for several minutes. She then developed a typical anginal attack, similar to those she experienced while walking, and had to sit up to get relief. The pain was substernal in location, and, according to the patient, differed definitely from the discomfort in the region of the heart described as symptom (2).

5. PALPITATION. During the first part of our study, palpitation was disregarded because it was seen in so many nervous or hypertensive patients who did not have the other characteristic symptoms of trepopnea. It was thought to be due to the fact that the heart lay upon the left chest wall and thumped against the ribs when the patient lay on that side. We now suspect that in a number of cases, this is not the mechanism of production of the symptom, because it may occur with the patient on the back when the apex impulse is neither seen nor felt, and may disappear as he turns toward the left when the apex beat becomes clearly visible and palpable. One patient who complained of palpitation when he lay on the back said that the "beating" disappeared as he rolled to the left anterior position. When it was pointed out, in this position, that the heart beat was clearly visible, causing the precordium to heave, he said "that is not what I feel; when I lie on my back, my heart bounces, it beats quietly when I lie this way." The complaint of "feeling the heart beat" was not, as a rule, dependent upon changes in rate or rhythm. We are tempted to believe that in many cases, an actual change in heart action occurred in certain horizontal positions, which produced unpleasant consciousness of the heart beat, and caused the complaint—"my heart beats hard."

6. **FATIGUE.** Eleven patients complained of fatigue; several said "I feel as though I had been running"; 3 felt dizzy as though they were going to faint; 1 broke out in a cold sweat. These symptoms occupy a prominent position in the minds of certain patients. They disappear when a favorable recumbent position is assumed. We believe they are frequent and definite enough to be classed as important subjective complaints. Two patients stated that on occasions when they had maintained an unfavorable position too long, this sense of weakness became so overpowering that they had to be helped into a sitting position, being unable to move.

Many other symptoms occasionally were mentioned (Table 1). If an individual was uncomfortable in two positions, the symptoms experienced were not always the same in both. Five patients were able to tell exactly when trepopnea first appeared, because they were forced by it to discontinue lying in a certain recumbent position which had previously been a favorite one.

The intensity to which the symptoms rose when an unfavorable position was maintained varied somewhat. Certain individuals in Group 3 became quite uncomfortable with dyspnea and precordial discomfort, but no matter how long they stayed in the unfavorable position, these manifestations did not reach a compelling level. Some subjects noted a spontaneous disappearance of the symptoms after they had become fairly severe, although the position was not changed. In Group 4, however, the discomfort increased progressively until the patients were forced to alter their recumbent position.

C. The Cardiovascular Characteristics of the Group. (Table 2.) Most of the patients had rheumatic or degenerative heart disease. In all but 6 the heart was considerably enlarged. In all but 3 there was a marked reduction of cardiac capacity; 17 actually were in congestive heart failure; 15 had permanent auricular fibrillation; 9 have died since the study was begun, in October, 1935.

One might expect to find that the position-preference pattern of a patient depended upon the type of cardiac lesion present; that all patients who were most comfortable prone, for instance, and least comfortable supine, would show a certain valvular lesion, a certain type of cardiac silhouette, or a certain type of cardiac failure. However, our data do not demonstrate the existence of such a correlation between position preference and any known cardiovascular characteristic. We cannot predict the lesion from the patient's position-preference pattern; or, knowing the type of failure predict the position he will prefer.

Certain factors often exaggerated trepopnea: an upper respiratory infection, the ingestion of a large meal, fatigue, or the appearance of congestive heart failure. Two patients developed this symptom when they suffered an acute coronary occlusion.

A patient may change from Group 3 (trepopnea of preference) to Group 4 (trepopnea of necessity) after a heavy meal. He may, for the first time, become unable to tolerate a certain recumbent position when he has a cold. As congestive heart failure disappears he may change completely his type of trepopnea or may lose entirely his discomfort in all recumbent positions. Some of our patients who have developed congestive heart failure have lost the ability to be comfortable in any recumbent position, and have had to sit up.

TABLE 2.—CARDIOVASCULAR CHARACTERISTICS OF 52 PATIENTS WITH TREPOPNEA.

Etiology.	Group 4.	Group 3.	Total.
Rheumatic	9	15	24
Degenerative	7	13*	20
Luetic	2	3	5
Congenital	1	0	1
Subacute bacterial endocarditis	1	0	1
Unknown	0	1	1
Total	20	32	52

* Two of these were moderately thyrotoxic.

Enlargement of heart.	Group 4.	Group 3.	Total.
Unknown	0	1	1
Slight	2	3	5
Moderate	5	15	20
Marked	5	11	16
Very marked	8	2	10
Total	20	32	52

Functional classification.	Group 4.	Group 3.	Total.
Class I	0	0	0
Class II-A	0	3	3
Class II-A to B	8	14	22
Class II-B	3	7	10
Class III	9	8	17
Total	20	32	52

One might summarize the cardiovascular characteristics of these patients by saying that most of them showed considerable cardiac enlargement, and a marked reduction of the functional capacity of the heart. However, there are a number of patients with large hearts and congestive failure who have neither trepopnea nor orthopnea. The explanation for this is not clear. No regularly occurring cardiovascular characteristics have been observed by which these patients can be differentiated from those with position preference; but in most, engorgement of the veins and liver was more outstanding than engorgement of the lungs.*

D. **Observations Concerning Trepopnea.** 1. **THE TIME INTERVALS.** When a patient moved from a favorable to an unfavorable position there was usually a latent period before the appearance of

* Recently, in one of our patients, pulmonary congestion disappeared and engorgement of the veins and liver occurred. Coincidentally trepopnea disappeared.

symptoms. This period varied from 10 seconds to 2 minutes (average about 20 seconds). The length of time which the patient could endure the unfavorable position varied from 30 seconds to a half hour. The symptoms usually disappeared almost immediately when a favorable position was resumed. When a patient with fully developed trepopnea remains in an unfavorable position too long, he may experience an alarmingly severe attack of dyspnea, from which he may not recover for 10 to 15 minutes. In these severe attacks the patient usually has to sit up to get relief; he is, as a rule, unable to recover comfort by merely turning to a favorable recumbent position.

2. THE RESPIRATORY PHENOMENA. These were variable (Chart II). Certain patients showed a rapid rise of their respiratory rate, to double the original and an apparent lessening in depth. Others

LEGEND FOR CHART II.

A bandage was placed around the chest with a rubber balloon beneath it. Variations of pressure in the balloon due to respiratory excursions of the chest were transmitted to a writing lever and recorded on a moving drum. Each section (A, B or C) is the respiratory tracing for 1 minute. All sections are not identical in length due to mechanical factors inherent in the kymograph. The comparative size of the waves is not necessarily an accurate indication of the comparative depth of breathing.

CASE 1.—J. G. Hypertension, trepopnea of necessity; 4 pillows under the head. A, Lying on right (best side). Respiratory rate 26, comfortable. B, Lying on left (worst side). Fourteenth minute, respiratory rate 44. Patient was forced to return to right 1 minute later by choking, smothering, a sense of pressure in the region of the heart and marked fatigue. After returning to the right, he became comfortable in 3 minutes. C, Six minutes after returning to right, respiratory rate 21, perfectly comfortable.

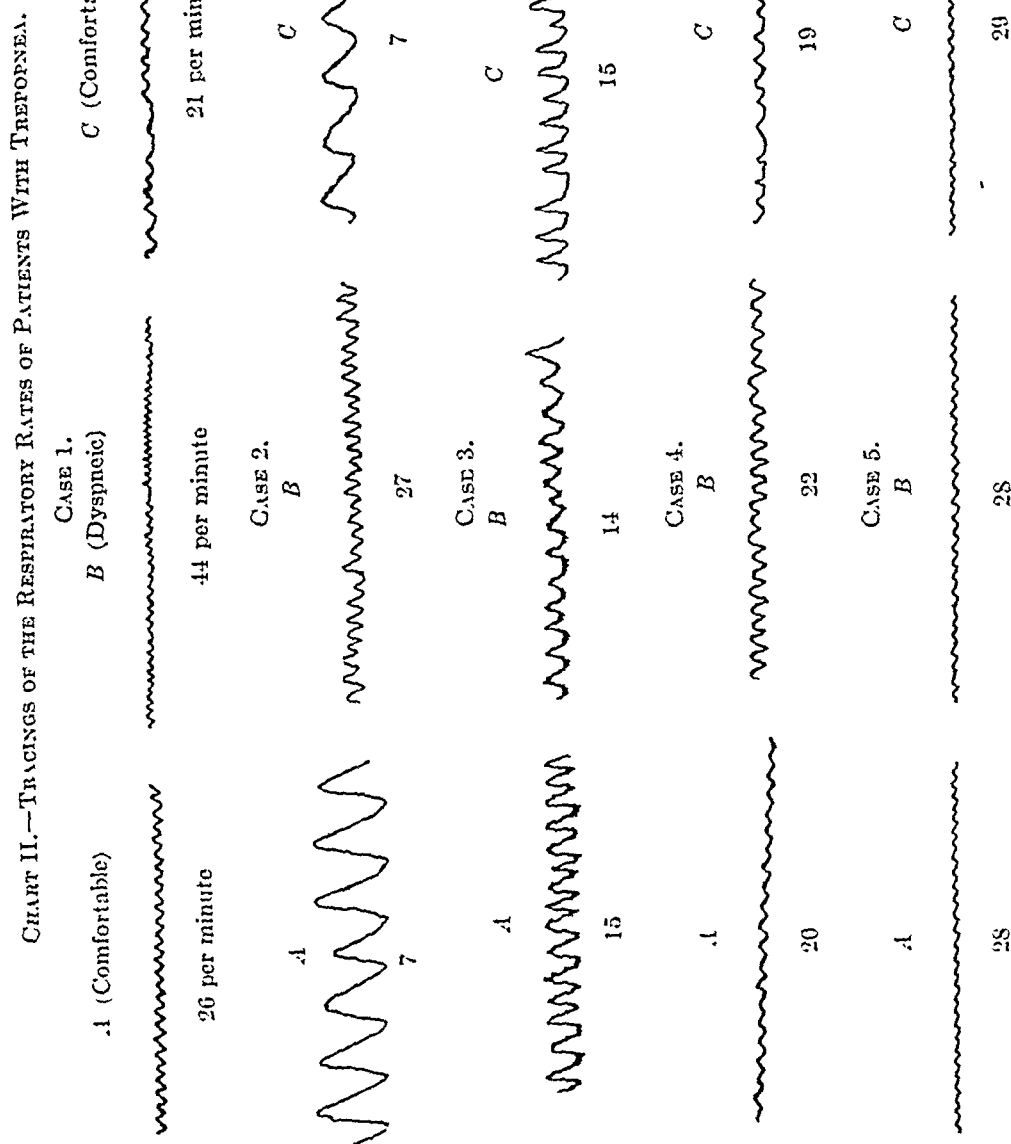
CASE 2.—H. B. Rheumatic heart disease, trepopnea of necessity. A, Lying on left (best side). Respiratory rate 7, comfortable. B, Lying on right (worst side). Ninth minute, respirations 27. Patient had to return to left 2 minutes later, because of smothering and marked weakness. C, Two minutes after returning to the left, respiratory rate 7, perfectly comfortable.

CASE 3.—L. A. Rheumatic heart disease, trepopnea of necessity. A, Lying on right (best side). Respiratory rate 15, comfortable. B, Lying on left (worst side). Ninth minute respiratory rate 14. Forced to return to right 1 minute later by inability to get the breath and a "heavy weight" over the heart. C, Lying on the right once more, perfectly comfortable. Respiratory rate 15. Despite a definite sense of "shortness of breath" when lying on the left, there was no increase in respiratory rate, and no obvious deepening of respiration.

CASE 4.—E. W. Rheumatic heart disease, trepopnea of choice. A, Lying prone (best position). Respiratory rate 20, comfortable. B, Lying supine (worst position). Fourth minute, respiratory rate 22. Returned to prone position because of choking, having to "pull hard" for breath and a weight across the upper sternum. C, Lying prone, inclined to the right. Eighth minute, perfectly comfortable, respiratory rate 19. Despite a definite sense of choking in the supine position, there was no marked acceleration of the respiratory rate.

CASE 5.—C. Z. Rheumatic heart disease, trepopnea of necessity. A, Lying on right (best side). Comfortable, respiratory rate 28. B, Lying on left (worse side). Respiratory rate 28, extremely uncomfortable. Forced to return to right by "something cutting off my air," restlessness and the heart "beating heard." Became comfortable 2 minutes after turning. C, Lying on right (best side). Fourth minute, very slight sense of "tightness" in the chest, but not really uncomfortable. Respiratory rate 29. Despite marked "dyspnea" when on the left, there was no change in respiratory rate, and no obvious deepening of respiration.

showed a change of facial expression from one of relaxation and comfort to one of anxiety and apprehension, and complained bitterly of dyspnea, but did not increase their respiratory rate. Moreover,



although spirometric records were not obtained, we feel quite sure that breathing was not deepened. If these observations are supported by careful measurement of minute volume, they indicate that the dyspnea which is the outstanding complaint of these

patients is a subjective sensation, which may or may not be accompanied by obvious change in the rate or depth of breathing. It may be that the dyspnea produced by exercise is a sensation which arises when ventilation exceeds a certain minute volume.⁵ However, this does not necessarily seem to be the case in dyspnea produced by changes in recumbent position, nor as we have subsequently learned, in the dyspnea caused by having an orthopneic patient lie flat in bed. In these last 2 instances, breathing becomes a conscious effort, but the facial expression may be the only objective indication of the degree of distress. Periodic breathing was commonly seen in these patients but we cannot be sure that this phenomenon was related to the assumption of a particular recumbent position.

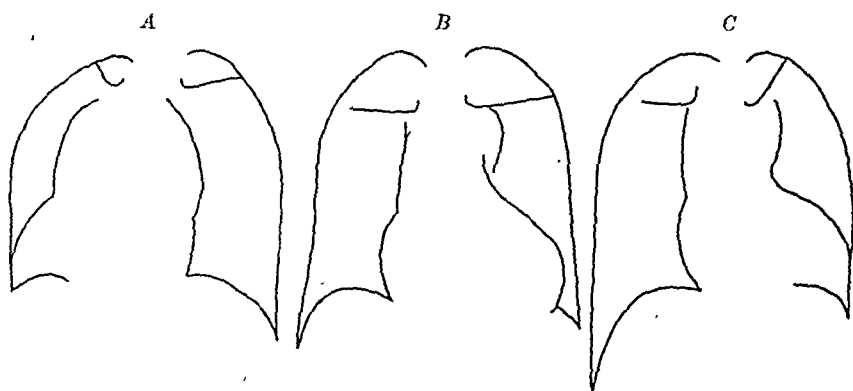


CHART III.—Orthodiagrams of a patient with degenerative heart disease and trepopnea of choice, showing marked movement of the heart, and definite change in shape of the supracardiac shadow, with change of position. *A*, Patient lying on right (best position). Heart against the right chest wall. Supracardiac shadow 11 cm. in width. *B*, Patient erect. Supracardiac shadow 7.5 cm. in width. *C*, Patient lying on the left (worst position). The heart has moved 6.5 cm. to the left, when compared to *A* and is now resting on the left chest wall. The supracardiac shadow is 7.8 cm. in width. The movement of the heart in this patient was about as great as any we have seen.

3. ROENTGENOGRAPHIC OBSERVATIONS. (Chart III.) On fluoroscopic study, 49 subjects fell into three groups: (a) 14 with no demonstrable heart disease and no trepopnea; (b) 15 with heart disease, without definite trepopnea; and (c) 20 with heart disease and real trepopnea. An orthodiagram was made of each individual, first as he lay on the right, and then on the left. Most cases were observed erect and supine, and sometimes prone. Changes in position of the heart were determined by measuring the distance from the lateral chest walls to the cardiac borders. We make no claim to extreme accuracy of measurement, but we feel quite sure that the following facts are correct:

(a) The heart moved considerably as the subject changed from one side to the other, as demonstrated previously by Cherchevsky.¹

Rumpf,¹⁰ and Pick⁹ with clinical methods, and by Hoffmann⁶ with Roentgen rays. Our figures are as follows: The smallest and largest movements of the right border were Group A, 0 to 6 cm.; Group B, 1 to 7.5 cm.; Group C, 0.5 to 6.5 cm. The smallest and largest movements of the left border were Group A, 2.25 to 7.25 cm.; Group B, 0 to 7 cm.; Group C, 1 to 6.5 cm. The average movement of the right border was Group A, 2.8 cm.; Group B, 3.4 cm.; Group C, 4 cm. The average movement of the left border was Group A, 4.5 cm.; Group B, 3.5 cm.; Group C, 4.1 cm. The two borders are discussed separately because there seemed to be a definite change in the width and shape of the heart in certain cases.

(b) The heart was not seen to move forward when the patient lay prone, or backward very much when the patient lay supine. The shadow of the anterior border usually was next to the anterior chest wall in both positions. As the subject changed from the erect to the supine position, the heart sometimes shifted to the left.

(c) We do not feel sure that we could detect striking changes in cardiac action caused by changes of position.

(d) As a subject turned from left to right, the supracardiac shadow usually showed a definite increase in width (Chart III). The average was 1.6 cm.; the maximum, 3.7 cm. So far as we could tell, this increase was due to an uncoiling of the aortic arch. The ascending aorta seemed to move considerably to the right, while the descending aorta tended to retain its original position. A comparison of the supracardiac shadow in the erect and left lateral positions showed it to be slightly wider in the latter, as a rule, especially in its lower part.

(e) The intensity of the symptoms produced was not proportional to the distance the heart moved. Certain cases in Groups A and B showed movement of the heart which was much greater than the movement of some of the cases in Group C, though the former had no symptoms and the latter had marked symptoms.

(f) The symptoms were not entirely dependent upon contact of the heart with the left chest wall; 5 of the hearts in Group C, 5 in Group B and 12 in Group A did not make contact with the left chest wall as the subject lay on the left.

(g) During inspiration, with the subject in a lateral position, the heart rose toward the midline, away from the side on which he lay. It sometimes moved several centimeters with each respiratory excursion. It looked as though the heart were slung in a hammock made by the dependent side of the pericardium, and was lifted as this hammock was pulled taut by descent of the diaphragm.

(h) Under the fluoroscope we could determine no reason why a given patient should like one recumbent position or dislike another.

(i) We confirm Howard's⁷ observation that the diaphragm has a greater respiratory excursion on the dependent side.

(j) Patients with the most severe degree of trepopnea could not tolerate their most unfavorable position long enough to permit the drawing of an orthodiagram. Their roentgenographic studies were made, if at all, after improvement of cardiac function had reduced the intensity of their symptoms, or had caused them to disappear.

4. VITAL CAPACITY MEASUREMENTS. The vital capacity has been tested in 52 subjects, in the sitting and in various recumbent positions; 14 had no evidence of heart disease; 14 had heart disease without trepopnea; 24 had heart disease with trepopnea. The method used to determine the vital capacity was that reported by other observers.^{5,2} The subject was given 3 tests in each position, and the highest was taken as the vital capacity. Our results give rise to the following comments:

(a) In patients with trepopnea the vital capacity did not tend to be greater in the most favorable than in the most unfavorable recumbent position. The actual figures are as follows: Of the 24 such subjects tested, in 6 the vital capacity was higher in the best recumbent position than in the worst, in 14 it was lower in the best position than in the worst, and in 4 it was equal in the two positions.

(b) After a patient remained in an unfavorable recumbent position long enough to become dyspneic, the vital capacity dropped markedly. There was no indication that the vital capacity drop caused the dyspnea or that the reverse was necessarily true.

(c) There seemed to be no very definitely significant difference between the vital capacity in the various recumbent positions. The figures are as follows for all 52 patients: When the vital capacities lying on the right, left and back were compared, the highest value was found on the left 31 times, on the right 23 times and on the back 17 times; there were 19 ties. The lowest value was found on the left 13 times, on the right 23 times and on the back 26 times; there were 10 ties. The vital capacity was tested in the prone position in only 21 of the 52 patients. It was the highest recumbent figure 3 times and the lowest 10 times, independent of the degree of comfort the subject experienced in that position. Thus our vital capacity figures tend to be greater on the left than on the right, and greater on both the right and left than in the prone and supine positions.

(d) The results obtained when vital capacity is measured vary so tremendously with the amount of will power which the subjects apply toward forcing a complete expiration, that small differences cannot be considered significant.

(e) We confirm in general the results of other workers^{3,4,7} that the majority of subjects show a higher vital capacity sitting than recumbent; and that on the other hand, certain patients have a higher vital capacity recumbent than sitting. It is interesting to note that none of the investigators state whether or not the patients

with orthopnea are the ones with lower recumbent vital capacity. Our figures are as follows in all 52 cases tested: the vital capacity was highest 35 times sitting, 15 times recumbent on the left, 11 times recumbent on the right, 6 times recumbent on the back and once in the prone position; there were 16 instances where 2 of these positions tied for the highest value.

These data show that trepopnea is not caused by a reduction of vital capacity in the unfavorable position.

5. POSITIONS WHICH ARE ASSUMED AT NIGHT BY INDIVIDUALS WITH AND WITHOUT TREPOPNEA.* (a) The normal: We have attempted to obtain a rough idea of the frequency with which hospital patients without trepopnea assume various recumbent positions. The method employed was to have the nurse make a record, at regular intervals during the night, of the position in which each patient in the ward was lying. On 40 adults who had no disease that should have caused trepopnea 1390 observations were made. They were found to lie on the left 305 times, on the right 410 times, on the back 618 times and on the abdomen 60 times. With few exceptions all the patients showed this same type of pattern. A simplified way of expressing it would read: left, 3 times; right, 4 times; back, 6 times; and abdomen less than once. These individuals were rarely aware of the amount of time they slept on the back; 6 of them said they had a preference for a certain recumbent position but their nocturnal behavior showed that their pattern was normal; 7 additional patients stated such a preference and showed that they actually had it. They will be discussed below.

(b) We made 2396 observations on 27 children, 5 without demonstrable heart disease, 17 with mild heart disease and 5 with severe heart disease with considerable cardiac enlargement. Those with normal hearts and those with mild heart disease had similar patterns, namely, left 5 times, right 7 times, back 6 times and abdomen once. Those with serious lesions with cardiac enlargement showed a different pattern, namely, left 5 times, right 9 times, back 3 times and abdomen once. Thus these normal children lay on the back less than the adults studied; moreover those with severe heart disease and cardiac enlargement lay much less on the back and much more on the right than children with little or no heart disease.

(c) With these observations as a background we can report upon 14 cardiac patients with trepopnea. The first patient said she could lie only on the right; she was observed 12 times on her right and never on the back, left or abdomen; no nurse ever saw her lying voluntarily in any other position. The second patient said he could not lie on the back, was moderately uncomfortable on the

* We are indebted to the nurses of the University and the Children's Heart Hospitals for collecting these data.

left and preferred the right; he was observed to lie 9 times on the right, 3 times on the left and never on the back. The third patient said she preferred to lie on the back inclined to the right, or on her abdomen; she could not lie on the left; she was observed lying on the back inclined to the right 10 times, and on the abdomen twice; she was not seen on the left. A fourth patient said she could not lie on the back or left and preferred the right, inclined forward; she was found lying prone 9 times and on the right once, but never on the back or left. A fifth patient preferred the right, was fairly comfortable on the back and could tolerate neither the left nor the prone position; he was found on the right 9 times, on the back twice and never in the left or prone positions. The sixth patient had acute coronary occlusion about 2 weeks previously. He could not lie on the left at first, and when watched was on the right twice, on the back 9 times and on the left not at all. As he improved he gradually became able to lie on the left, so that during the next six nights his positions were: right, 18; back, 38; left, 8. The seventh patient said he could not lie on the left; he was recorded to lie on the right 12 times, on the back 20 times and on the left twice. The eighth patient said she could not lie on the left; she was reported on the right 7 times, on the back 4 times, on the left once. Later as she improved the following figures were obtained: right, 9 times; back, 6 times; left, 5 times. The ninth patient had acute coronary occlusion and did not like the left. He was watched continuously for 24 hours; he spent 11 hours and 10 minutes on the right, 11 hours and 15 minutes on the back and 1 hour and 35 minutes on the left. Five other patients were observed who did not bear out their stated position preference by their nocturnal behavior. When tested while awake, their symptoms were definite but not cogent. One, the tenth case, said that she could not lie on the right. She was recorded on the right 6 times, on the back 10 times and on the left 4 times. The eleventh said she did not like to lie on the back. She was recorded on the right 47 times, on the back 29 times, on the left 37 times and on the abdomen 35 times. The twelfth said he could not lie on the back and disliked the left. He was found on the right 3 times, on the back 3 times, on the left 4 times and prone twice. The thirteenth said her worst position was supine and her best, prone. She was found on the right 6 times, supine 11 times, on the left twice and prone 12 times. The fourteenth, a girl with rheumatic heart disease, 7 months' pregnant, preferred the right or prone positions and could not tolerate the left; she was found on the right 3 times, supine 3 times, on the left twice and prone 5 times. A factor which complicated the interpretation of the foregoing observations was that most of these sick cardiac patients desired some elevation of the head at night. Thus all but the first, fourth, fifth, eleventh and twelfth had the head of the bed elevated from 30 to 45 degrees when their

nocturnal positions were charted. Patient 4 was observed at another time with the head of the bed elevated 30 degrees and was found on the right 8 times, on the back 4 times, on the left twice and prone 7 times. Thus, elevation of the head of the bed enabled her to tolerate certain positions which she had not assumed when horizontal. We conclude that patients with trepopnea of an advanced degree show a definite difference from the normal nocturnal position pattern, and do not lie at night on the side upon which they say they cannot lie. As the symptom gets less marked, they tend to resume the normal nocturnal pattern. Those who do not really have cogent symptoms, even though they are uncomfortable on a given side during waking hours, are found to assume that position during sleep.

(d) Certain patients without heart disease stated that they had a definite preference for a certain recumbent position and the modification of their nocturnal position pattern confirmed their statement. Two were asthmatics; 1 could not lie on the left and showed a pattern of R-3, B-13, L-0;* one could not lie on the back and showed a pattern of R-31, B-9, L-16. A third had ulcerative colitis and said if he lay on the left it precipitated a bowel movement; he showed a pattern of R-10, B-2, L-0. A fourth patient with pulmonary tuberculosis and artificial pneumothorax on the left could not lie on the side of the pneumothorax; he showed a pattern of R-3, B-9, L-0. A fifth with an intraabdominal abscess could not lie in any position but on the back; he showed a pattern of R-1, B-76, L-0. A sixth patient with malignant metastasis to the spine could not lie on the right and showed a pattern of R-0, B-2, L-6, abdomen 4. The seventh patient said he could not lie on the back; we have no adequate explanation for this; he showed a pattern of R-11, B-0, L-1. Three very fat women apparently had real trepopnea but were not watched at night. The first liked the right best and could not lie on the left. The second liked the back best, the abdomen next and could not lie on either side. The third liked to lie on her abdomen best, and on the back next. She could not lie on either side.

(e) Certain patients who might have been expected to prefer certain recumbent positions to others did not. One patient with myelogenous leukemia with an immense spleen showed no preference. One patient with tremendous neoplastic hepatic enlargement had a pattern of R-7, B-10, L-2. Three women, pregnant, near term, showed some modification of the normal pattern, *i. e.*, the first, R-9, B-9, L-8; the second, R-15, B-7, L-3; the third, R-5, B-12, L-2, abdomen 2 (inclined to the right).

6. CERTAIN CARDIOVASCULAR PHENOMENA WERE STUDIED DURING THE ASSUMPTION OF THE UNFAVORABLE POSITION. (a) *The Heart Sounds.* In a few instances, systolic murmurs seemed to

* R, right; B, back; L, left.

become louder after the patient had maintained the left lateral position for a few minutes. The fact that the mitral diastolic murmur is intensified by lying on the left is well known. In the past we have believed this to be due to the closer approximation of the heart to the stethoscope on the left chest wall.

(b) *The Pulse.* The rate, rhythm and volume of the pulse showed no consistent change. Pulse tracings have not been taken. One individual showed a pulsus bigeminis which lasted for 2 minutes each time he turned to the left. If he maintained the position, the arrhythmia disappeared. The occurrence of a few extrasystoles when a patient assumed an unfavorable position was not uncommon.

(c) *Blood pressure changes* have been inconstant, and difficult to evaluate. A definite rule may develop as observations multiply, but it is not as yet evident.

(d) *Electrocardiographic records* were taken in 7 patients. They showed no change in an unfavorable position which could be confidently attributed to a change in cardiac action.

(e) *The venous pressure* has not been taken. Observation of the appearance of the cervical veins suggests that a rise in venous pressure is not a regular occurrence when an unfavorable position is assumed. Four patients who complained of a fullness in the head and a feeling of the eyes bulging from their sockets in certain recumbent positions showed an increased prominence of their cervical veins.

(f) *Cardiac output measurements* have thus far been made in only 1 subject, a man aged 34, without evidence of heart disease, whose heart moved 6 cm. as he changed from one side to the other. He had no trepopnea, though he was sometimes conscious of throbbing in the chest as he lay on the left, and usually went to sleep best lying on the right. Four determinations were made by Dr. Isaac Starr, using the method described by him.¹¹ The first, with the subject lying on the left, showed an output of 3.24 liters per minute. The second, with the subject on the right, showed an output of 5.37. The third, with the subject still on the right, showed an output of 4.82. The fourth, with the subject on the left again, showed an output of 4.37. The pulse counts, respiratory rates, blood pressure readings and oxygen consumption measurements showed the subject to be in a satisfactory basal state throughout all the determinations. The pulse varied from 56 to 60 per minute. The respiratory rate varied from 9 to 7.5. The blood pressure varied from 100/76 to 88/62. The oxygen consumption in cubic centimeters per minute was 257.8, 267.2, 258.6 and 263.2, respectively, during the 4 determinations.

E. Discussion of the Mechanism by Which Trepopnea Might Be Produced. The conclusion seems justified from the observations we have reported that this phenomenon cannot be accounted for by vital capacity changes nor by variations in relative levels of

right auricle and respiratory center (factors which have been advanced as explanations for orthopnea). We investigated the possibility that it might be due to pleural fluid. Four of the 52 patients had pleural effusion on the right, and preferred lying on the right. However, in 28, physical examination supplemented by Roentgen ray study failed to demonstrate the presence of fluid in either side of the chest, and 3 others that came to necropsy had no definite effusion in either pleural cavity. The remaining 17 cases had no physical signs of a pleural collection at the time they were studied for trepopnea, but Roentgen ray studies were not made. These observations indicate that pleural fluid does not account for this phenomenon. This conclusion is supported by the fact that several patients not in this group, with fairly large pleural effusions, did not have trepopnea.

The most likely possibility that we can visualize is that trepopnea is due to movement of the heart in the thorax as the patient changes position, and that this movement causes pressure upon certain mediastinal structures which gives rise to the signs and symptoms. In support of this hypothesis, the following might be mentioned:

(a) Roentgen ray studies show that the heart does move quite markedly as an individual changes from one recumbent position to another.

(b) Observations at the necropsy table have shown us that a large heart moves with considerable force, as the position of the body is changed; and that it rests heavily upon the structures beneath it.

(c) A study of mediastinal anatomic relationship (to be discussed below) and a consideration of the physiologic effects of pressure on certain structures in the neighborhood of the heart suggest that the symptoms of trepopnea could be produced by the movements of a large heart in one direction or another.

(d) If the heart of a dog is mobilized by severing its attachments to the diaphragm so that it will move with change of posture, its action can be markedly embarrassed by placing the animal in certain recumbent positions, which tend to obstruct the great vessels.

(e) Very slight changes in the position of the dog cause marked changes in the action of the heart. Very slight changes in the position of a patient may cause the appearance or disappearance of very distressing symptoms.

(f) Rumpf,¹⁰ Pick,⁹ Hoffmann,⁶ and Van Zant¹³ have described a few patients with unusual mobility of the heart in the mediastinum ("das bewegliche Herz"). These patients suffered dyspnea and precordial discomfort when lying on the left. An unusual proportion of them were fat people who had recently taken a hunger cure. One patient had heart disease but this fact was not given much prominence, since the author was studying cardiac mobility. This syndrome suggests that an unusual degree of movement of a normal

heart is capable of causing the symptoms of trepopnea. The greater frequency of such symptoms in patients with heart disease might be explained on two grounds: (1) A large heart probably moves with greater force than one of normal size; and (2) a weak heart is apt to be disturbed more readily by impediments to the mediastinal vascular channels than is one with normal power.

The foregoing thoughts led to an investigation of mediastinal anatomy to determine which structures might be affected by movement of the heart. Many possibilities presented themselves:

(a) In certain cases of mitral stenosis the left bronchus is known to be reduced in caliber by pressure from the left auricle. Possibly a slight further reduction of the bronchial lumen by pressure from an enlarged heart might cause dyspnea in much the same way that obstruction of one nostril will cause breathlessness during exercise.

(b) Pressure by a large heart upon the lung itself or upon the nerves in it might cause respiratory distress.

(c) The aortic arch makes an arc with a fairly large radius when the patient lies on the right and the heart falls toward the right. When the patient lies on the left or back the heart moves so as to reduce the radius of the arc. This might increase the work of the left ventricle. It might also produce throbbing in the chest, since under similar circumstances the heart of a dog will "bounce" with each heart beat.

(d) When an individual lies on the side the act of inspiration raises the heart, as described above, sometimes a distance of several centimeters. When the heart is large this should cause extra work for the diaphragm as it descends, and might bring on dyspnea.

(e) The fact that a light grasp of the left ventricle of a dog causes a marked reduction in blood pressure suggests the possibility that the force with which a large heart presses against the chest wall might be enough to cause symptoms. However, not all hearts which lie on the chest wall give rise to symptoms, and hearts which give rise to symptoms do not all press against the chest wall.

(f) The one possibility which seems most probable, however, has to do with obstruction of the venous return from the lungs. The following facts support this explanation: First, an increase of pressure in the pulmonary circulation is known to give rise to respiratory reflexes⁵ and therefore might cause the respiratory symptoms of trepopnea. Second, a relatively small amount of force would be required to obstruct blood flow through the pulmonary veins and left auricle, because of the low pressure within these structures. Third, anatomic considerations suggest that this force could be readily supplied by the movement of a large heart in the mediastinum. If one inserts a finger in the lower end of the esophagus of a supine cadaver with cardiac enlargement, before the chest is opened one can appreciate that the heart rests quite heavily on the structures behind it, *i. e.*, the pericardium, spine and aorta. The

left auricle and pulmonary veins lie posteriorly, and might readily be compressed between the heart and spine, or they might be kinked as they enter the pericardium, by a twist of the heart. Of all the pulmonary veins, the large left inferior vein is situated where it could be obstructed most readily. Moreover, its obstruction could be brought about most adequately if the subject lay on the back, inclined toward the left (*i. e.*, in the position most frequently productive of symptoms in trepopneic patients). Pressure of the heart on some structure behind it is especially suggested as a cause for the symptoms in those patients whose most comfortable position is the prone one, a position which would not seem conducive to free breathing, but which would have the one virtue of removing pressure from the left auricle and left inferior pulmonary vein.

The less common symptoms might also be accounted for by the movement of the heart: A coronary artery might occasionally be kinked near its orifice by a twist of the heart on its pedicle, thus causing anginal pain.¹⁵ The patient who experiences abdominal pain in a certain position might be suffering from obstruction of the inferior vena cava or hepatic veins. Those individuals who have congestion of the face, fullness in the head and bulging feelings in the eyes may have an obstruction of the superior vena cava. Movement of the heart might also account for the fact that certain patients when sitting up are dyspneic leaning back, and comfortable leaning forward.

The variations we have observed in the side which is preferred and in the symptoms which are produced by lying in certain recumbent positions, might be accounted for by anatomic and pathologic variations in mediastinal structure. These differences in symptoms and in position preference suggest that, if altered mediastinal relationships cause trepopnea, the structures involved are probably not always the same in each instance. The fact that certain patients with congestive failure and marked cardiac enlargement can lie comfortably in all recumbent positions is difficult to understand. However, no other available explanation seems to account for the phenomenon of trepopnea as adequately as the hypothesis that it is due to movement of the heart in the thorax.

Blumgart and Ernstene have reported that many cardiacs are comfortable with the head flexed on the chest and are uncomfortable with the head extended. Though their deductions from this observation⁴ have been questioned,⁵ the observation itself has been confirmed by us. We might add that this takes place in some patients as they lie on the side as well as when they lie on the back. In the cadaver it can be shown that the aortic arch and pericardium are fixed to the deep cervical fascia, and that these structures can be pulled up as much as several centimeters, when the head is extended. This might alter mediastinal relationships sufficiently to cause symptoms on the basis of the hypothesis we have outlined.

F. The Implications Which Result From These Observations.

1. CONCERNING THE MECHANISM OF PRODUCTION OF ORTHOPNEA:

We wish to point out (a) that no entirely satisfactory explanation for orthopnea is available, (b) that orthopnea and trepopnea seem related, (c) that the latter is not explainable on the basis of: Vital capacity changes,⁵ hydrostatic factors of anatomic origin,³ or variations in relative levels of right auricle and respiratory center,⁴ (d) that this casts additional doubt upon the correctness of these explanations for orthopnea and (e) that the hypothesis we have outlined as a possible explanation for trepopnea, may help to explain orthopnea also. Point (b) might be discussed in a little more detail: Although trepopnea may appear in a patient long before orthopnea develops, and although some patients are orthopneic but have no trepopnea, a relationship between orthopnea and trepopnea is suggested by the following: (1) The symptoms which are produced by assuming an unfavorable recumbent position are the same as those which are experienced by an orthopneic patient when he lies flat in bed, namely, dyspnea and precordial oppression. Moreover, the dyspnea in both may be primarily a subjective sensation, as described above. (2) Both orthopnea and trepopnea may change as cardiac failure appears and disappears, and both show the same variation between "necessity" and "preference." (3) These two phenomena are seen in the same general group of patients. (4) They are frequently seen combined in 1 patient, *i. e.*, an individual if uncomfortable lying flat on his back or on the left may be able to achieve comfort either by sitting up or by remaining flat and rolling to some other recumbent position such as the right lateral or the prone position. This point, in addition to suggesting a relationship between orthopnea and trepopnea, furnishes evidence which is extremely damaging to an accepted explanation for the former: When dyspnea, caused by lying supine, can be relieved by assuming either of two other positions, one which increases the vital capacity and the other which does not, it is difficult to believe that vital capacity changes explain the relief.

2. CONCERNING THE MECHANISM OF PRODUCTION OF NOCTURNAL DYSPNEA. The reason why cardiac patients should wake up in the middle of the night with "acute left ventricular failure,"^{5,8,11} when their hearts should be working at a minimum rate, has long been a mystery. We have the following evidence to present on this point: (a) We have witnessed 1 severe paroxysm of dyspnea, and have been told by our patients of 5 others which were produced by maintaining an unfavorable recumbent position too long. Many mild attacks have been observed which have forced the subject to sit up to get his breath. A typical story was told by 1 of our patients with trepopnea, who was uncomfortable when lying on the left side. We asked him to find out how long he could maintain that position when he went to bed. The next time we saw him he

reported that he had stayed on that side for a half hour that night. He had then become so dyspneic and weak that he was almost unable to move. His wife assisted him to a sitting position, and after 15 or 20 minutes of cough, dyspnea and severe precordial discomfort he recovered. She made him promise not to try it again. (b) Many patients with trepopnea have been questioned about nocturnal dyspnea. Most of them state that they wake up at once when they turn to an unfavorable recumbent position and can never tolerate it long enough to bring on a bad attack, even when asleep. Our observations of their nocturnal behavior cast doubt upon such statements by some individuals. However, only 4 of our patients with real trepopnea have had attacks of severe nocturnal dyspnea. (c) We have not studied enough patients with paroxysmal nocturnal dyspnea to be able to say whether, as a group, they do or do not routinely show trepopnea. (d) A few patients with very slight evidences of trepopnea have described attacks of severe dyspnea which occur at night and wake them from sleep. They said these seizures occurred only when they were on the left. Two volunteered this information without being questioned. One of these was a physician. The other was a colored man who came to the clinic with the chief complaint of nocturnal attacks of dyspnea which he termed "witch ridin' spells." Both he and his wife were certain they were caused by his lying on the left side. The evidence concerning the relationship of trepopnea and paroxysmal nocturnal dyspnea might be summed up by saying that: Severe paroxysms of dyspnea can be produced by lying in an unfavorable recumbent position too long. Paroxysmal nocturnal dyspnea might therefore conceivably be caused by a patient rolling into an unfavorable position while asleep and not waking up until cardiac embarrassment became severe. That this mechanism actually operates has not been demonstrated. If it does, the evidence at hand suggests that the individuals who suffer are those with mild rather than severe types of trepopnea.

3. CONCERNING THE REASON WHY PLEURAL EFFUSION IN HEART DISEASE IS AS A RULE MORE MARKED ON THE RIGHT THAN ON THE LEFT. Steele and Stengel¹² suggested that pressure on the azygos vein might account for this fact. More recently Dock³ has invoked "hydrostatic factors of anatomical origin" to account for it. He states that most cardiac patients prefer lying on the right to lying on the left because of consciousness of the apex beat in the latter position. Thus the right side, being more frequently dependent than the left, has the higher pulmonary venous pressure, and therefore the greater tendency to transudation of fluid. There are other points in his argument which we will not recount. We have the following factors to add: (a) There are symptoms, much more cogent than the "consciousness of the apex beat" referred to by Dock, which cause certain cardiac patients to prefer the right to

the left. (b) A few patients prefer to lie on the left and a few individuals collect more fluid on the left. (c) We have found a few patients with right-sided effusions who have preferred to lie on the right, but we do not know which came first, the preference or the effusion. In 1, tapping of the effusion enabled her to lie on the left with much more comfort. (d) We have seen 1 cardiac patient with a right pleural effusion who had no trepopnea. The crucial observation has yet to be made, *i. e.*, do those who prefer the right later develop right pleural effusion, and do those who prefer the left later develop left pleural effusion?

4. The only source from which we have been able to obtain literature on trepopnea was a patent medicine advertisement in a Philadelphia newspaper. The clipping was sent to us simultaneously by 2 physicians who knew of our observations. The caption of the advertisement reads "Don't sleep on left side, affects heart. Right side best." Almost every physician has heard the statement "It is bad for your heart to lie on the left." Probably most of them have regarded it as a mere superstition, possibly due to cardiac consciousness. The observations reported in this paper suggest that this bit of folklore, like many others, may be based upon a modicum of fact. Its incompleteness is illustrated by the story of 1 of our patients who never realized he had real trepopnea until one day a druggist told him it was "bad for his heart" to lie on the left. That night he lay on the right. Before long he became so weak and dyspneic that he could barely attract the attention of his mother in the next room, who came in and revived him. He was one of those individuals who can lie on the left or prone, but who cannot lie supine or on the right.

5. The intensification of a mitral diastolic murmur by having the patient lie on the left has been rather generally assumed to be due to the fact that this position brings the heart closer to the left chest wall. However, this assumption may be only partly correct. Other significant factors may be (a) a change in blood flow through the mitral valve and (b) an actual distortion of the mitral orifice by external pressure on the left side of the heart.

6. If our preliminary observations are correct it may be necessary for students of cardiac output to state the exact recumbent position in which their subjects lie when tested.

7. The question arises as to whether knowledge of this phenomenon will have any bearing on the treatment of patients with heart disease. Since those with fully developed trepopnea will not lie on the unfavorable side, it seems that they have taken care of themselves for years without the doctor's help. It might be well, however, in nursing a cardiac patient, especially if he is narcotized or unconscious for any reason, to be cognizant of the possible existence of this phenomenon. The order "turn the patient from side to side every hour" may have to be modified. Moreover, it may

be possible, if our speculations prove correct, to avoid attacks of nocturnal dyspnea, by making it impossible for a patient with this condition to lie on the unfavorable side. This might be accomplished by some sort of harness, by the judicious placing of pillows, or by sewing a hard object into the night clothes on the side to be avoided.

Summary. 1. Certain cardiac patients who are able to lie comfortably in one recumbent position cannot tolerate another.

2. They usually prefer the right and dislike the left, but there are many variations.

3. Dyspnea and precordial discomfort are the most common symptoms which are experienced in one horizontal position and relieved by assuming another. Cough and anginal pain are less frequent. Fatigue, dizziness and palpitation are also described. These are the same symptoms which lead an orthopneic patient to sit up.

4. Patients with this syndrome usually show considerable cardiac enlargement and definite reduction in cardiac functional capacity. The symptoms may change in intensity as the clinical condition of the patient changes. There is no apparent correlation between the position the patient prefers and any known cardiovascular characteristic, such as type of lesion, type of failure or shape of heart.

5. Observation of patients in their unfavorable recumbent positions shows that their complaint of dyspnea is probably a subjective phenomenon, a sense of suffocation, which may or may not be accompanied by obvious increase in rate or depth of breathing. This is also true of orthopnea.

6. Roentgenologic study shows that the heart may move considerably as a patient changes from one side to the other; that the intensity of symptoms is not proportional to the distance the heart moves; that the shape of the heart and aortic arch may change markedly as the subject changes position; and that, with the patient in lateral decubitus, the heart is lifted during each inspiration, sometimes a distance of several centimeters.

7. The vital capacity does not tend to be greater in the most favorable recumbent position than in the most unfavorable one.

8. Patients in whom this phenomenon is marked do not assume their most unfavorable position at night, even when asleep. Those in whom it is less well developed are sometimes found in an unfavorable recumbent position during sleep, although they may deny that they can tolerate this position.

9. Observations of the pulse, the arterial pressure, the cervical veins and the heart sounds have not as yet been productive of helpful information.

10. Electrocardiographic tracings have failed to show a change

in an unfavorable position which can be attributed confidently to a change in cardiac action.

11. One subject without heart disease or preference for any particular recumbent position showed a lower cardiac output on the left than on the right.

12. Change of position of the heart with distortion of the large vascular channels in the mediastinum is suggested as a possible cause for this phenomenon. The venous return from the lungs might readily be obstructed by this mechanism.

13. These observations may help to explain the mechanism of production of orthopnea and paroxysmal nocturnal dyspnea.

14. We have named this phenomenon "trepopnea" for the sake of brevity, even though it does not express the concept adequately.

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THE ORGANIC BACKGROUND OF SOME CASES OF SPASMODIC TORTICOLLIS.

REPORT OF CASE WITH AUTOPSY.

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THE problem of spasmodic torticollis has fascinated neurologists for many years, but its solution is still far off. Gradually there have evolved two schools of thought: the organic, which maintains that all cases of spasmodic torticollis have their basis in destructive lesions of the basal ganglia system; and the psychogenic, which maintains that most cases of this sort are due to psychogenic factors

caused by profound disturbances in the emotional life of the patient. The truth lies probably between these two extreme points of view. Some cases have an organic basis, and others a psychogenic background. It is even probable that both factors are operative in some cases, in view of the well-known influence which emotional stimuli have on organic conditions of all sorts. Because of the extreme divergence of the two schools of thought concerning the background of spasmodic torticollis, it seems wise to collect the evidence in support of one view or the other from time to time in order to clarify the problem. Furthermore, the very state of flux of the entire problem demands that evidence for or against one or the other viewpoint be recorded. Such an opportunity was given us recently in a case of spasmodic torticollis which had existed for many years, in which there were marked changes in the basal ganglia system on histologic examination.

Case Report. *Spasmodic torticollis for 47 years in a man 90 years of age. Mild evidences of choreo-athetosis in upper limbs. No change in pattern or increase in severity over many years. Striatal pathology. History.* W. B., a white male, aged 90, was admitted to this hospital, December 16, 1900, at the age of 55, because of a marked depressive trend which had led him to attempt suicide. The family history was negative. The patient himself had been quite well until 1888. He had been a skillful gymnast as a young man, and from the age of 25 had been constantly employed by the Philadelphia Fire Department. In 1888, he was struck in the right eye while at a fire and the eye became sightless. Subsequent to this accident he developed a tremor of the head and neck which gradually became worse but did not prevent his continuing his work as a fireman. On August 23, 1900, he was struck on the back of the neck with a live wire and was severely burned. He fell some distance and was unconscious for about 3 hours. No increase in the spasmodic movements of his head was observed after this mishap. As the burn failed to heal properly, he became depressed, apprehensive and suspicious and in December he was placed in the hospital to prevent a repetition of his one attempt to hang himself.

Physical Examination. The patient was a well-nourished, well-developed male. The hair was scanty. The chest was moderately emphysematous. The heart was not enlarged; the sounds were of poor quality, but there was no murmuring. The radial pulse was soft and compressible. The blood pressure was 130/90. The teeth were in poor condition with many cavities.

Neurologic Examination. The right eye was blind. The left eye showed a marked arcus senilis and a small pupil which reacted promptly to light and accommodation. Movements of the left eye were full in all directions. There was flattening of the right face, but the mouth did not open very widely at best. The right shoulder was decidedly lower than the left. The tongue was protruded in the midline, but after a few seconds showed slow athetoid movements, and a tendency of the tip to point to the right. There was a coarse tremor of the tongue which became more noticeable after protrusion for some moments.

The motor system showed definite impairment. The head was tilted to the left with the chin pointing to the right shoulder. This was not a constant position; at times it was held straight. Rotary movements of the head on the shoulder were done fairly well to the right and were very much more limited to the left. Hyperextension of the head was possible but limited. The right shoulder drooped and upon shrugging moved

through a much smaller arc than the left. In addition to the position of the head there were many movements of interest. The fundamental state was a coarse tremor of the head which was almost constantly present but which was aggravated on motion, on reading, or on emotional disturbance of any nature whatever. This was a nodding movement of the head to and fro. In addition there were quick choreiform twitchings which caused a sudden hyperextension of the head, pulled it suddenly backward and tilted the chin in the air. At times these movements caused a sidewise motion of the head. In addition there were slow athetoid-like movements of the shoulders, probably through action of the trapezius. There was a coarse tremor of the hands on extension and some ataxia, but this was not pronounced and was not an important feature. When the patient stood with arms by his side, however, one might observe slow, torsion-like movements of the head and choreiform movements of the hands, fingers and forearms. Athetosis was not as noticeable in the hands or arms as in the head, but was sometimes seen. The biceps, triceps, radial, patellar and ankle jerks were hyperactive and equal. There was no Babinski in either foot. No Gordon, Oppenheim or Chaddock was found. The station was normal. There was no incontinence of urine or feces.

Laboratory Reports. Repeated blood counts and blood chemistry were normal. The urine was negative. The blood Wassermann and Kahn tests (1934) were negative.

Course. The patient remained in the hospital for the rest of his life with little change in his mental condition except that he became increasingly reticent and his memory became worse. The neurologic manifestations likewise remained essentially unaltered through the years. The peripheral vessels became palpably sclerotic, the heart was occasionally irregular and in later years syncopal attacks developed. The highest systolic pressure ever observed was 160. The urea nitrogen was elevated (36.8 mg. %) on one occasion about a year before his death and small amounts of albumin with a few casts were often found in his urine. He sustained a fracture of his right hip November 30, 1935, and died suddenly the following day.

There was no change in the nature of the torticollis during his years in the hospital. For the most part the head was held in a position of lateral rotation and flexion to the left; but more and more it tended to be pulled backward (Fig. 1). As on his original admission the movements were spasmodic. They were slow, athetoid-like movements and were associated with athetoid movements in the fingers and other parts of the body. At no time during the period of confinement was there any evidence of remission from the spells of torticollis.

Gross Brain. The brain (postmortem examination 3 hours after death) weighed 1510 gm. There was thickening of the pia arachnoid over the cerebral hemispheres. The frontal and parietal gyri were moderately atrophic. The vessels of the circle of Willis were moderately sclerotic.

Microscopic Studies. Routine sections were made through all parts of the cortex. Serial sections were made through the entire basal ganglia system. The sections were stained with toluidine blue and the Weil modification of the Weigert stain.

Cortex. The pia arachnoid was fibrotic and thickened. It was adherent to the cortex in a few places. There were no signs of inflammatory involvement of the meninges. The cortical architecture was well preserved in all areas. In the frontal areas there was a scattered loss of cells in the Lamina Pyramidalis (III) but no more than was to be expected in a man of 60. There was a moderate hyalinization of the cortical arterioles in the frontal cortex.



FIG. 1.—Patient showing the typical posture of the head held in extension. Lateral movements were occasionally seen.



FIG. 2.—There is a slight reduction in size of the head of the caudate nucleus. Weil stain.

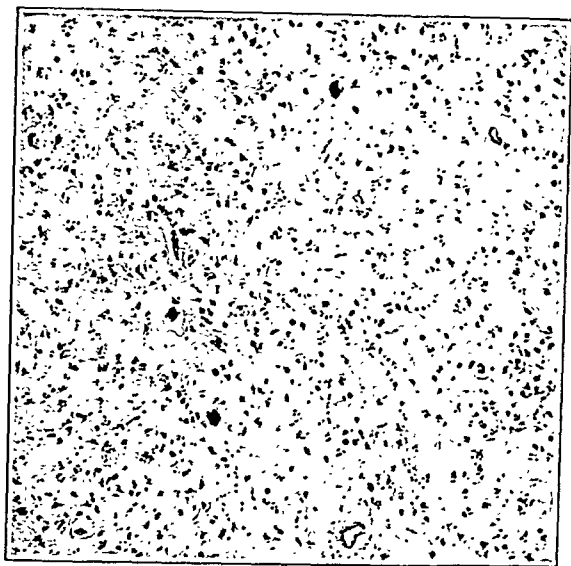


FIG. 3.—Low-power photograph showing only two large ganglion cells in the putamen. These cells are reduced in number. Toluidine blue stain.

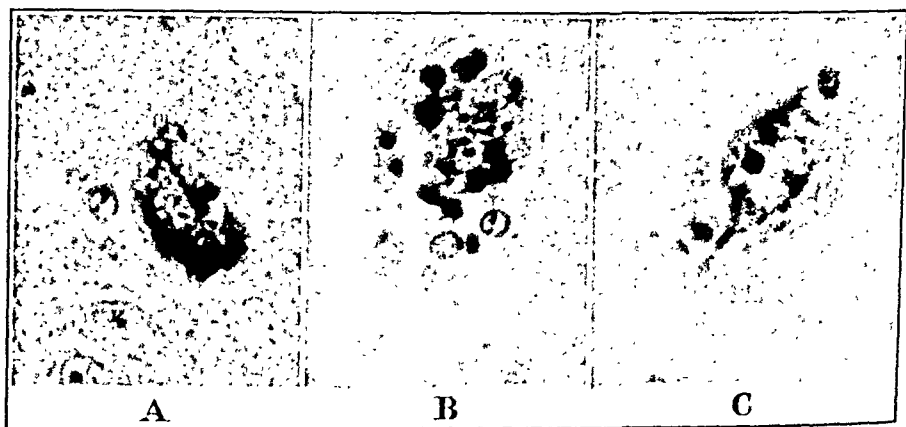


FIG. 4.—Characteristic cell changes in the large ganglion cells of the *neo-striatum*. *A*, shows a large ganglion cell from the putamen. The nuclear definition is lost, the cytoplasm is hyperchromatic. A few small cells nearby show cytoplasmic swelling and pallor of the cytoplasm. In *B* is seen a large ganglion cell of the putamen undergoing neuronphagia. The cellular definition is indistinct. In *C* is a large ganglion cell from the caudate nucleus. The nucleus is swollen and eccentric, the cytoplasm frayed, the Nissl substance lost. Toluidine blue stain.

Neostriatum. There were severe changes in both the putamen and caudate (Figs. 2 and 3). Both nuclei seemed equally affected. Both the small and large ganglion cells seemed diseased, but the large cells were more involved than the small. Some low-power fields contained only a single large cell; others contained from 1 to 3. All the large ganglion cells were diseased (Fig. 4). The nucleus was usually shrunken; sometimes it was swollen. The nucleolus not infrequently was swollen and took a pinkish tint. Often the nucleus was excentrically placed at the periphery of the cell. The nuclear membrane was intact in most of the cells; sometimes it was not visible. For the most part the nucleus stained lightly, but now and then one encountered a pyknotic nucleus. The cytoplasm was severely diseased in all the cells. The nature of the damage varied from cell to cell. Usually the cytoplasmic membrane was intact, but in some cases it was gone. The Nissl substance was completely absent in most of the cells; in others it was pulverized and usually at the cell periphery. The cytoplasm was shrunken. Vacuoles of varying size and number were present in all the cells. All the cells also contained yellow lipoid pigment. In some this was very abundant, filling the entire cytoplasm; in others it was not very abundant. Neurophagia was quite active in many cells. Sometimes a ganglion cell was entirely replaced by glial cells. The small ganglion cells stained very lightly. The nucleus was swollen and the cytoplasm of every cell filled with a coarse yellow pigment. The perineuronal spaces were swollen and distended.

The vessels of both the caudate and putamen were in surprisingly good condition. There were mild fibrotic changes in the arteriole walls, but no true sclerosis. One vessel showed perivascular infiltration with large round cells. Small granules of calcium, both discrete and coalescent, were found in both the putamen and caudate.

Weil stains showed a definite decrease in size of both the caudate and putamen. There were a few large lacunæ in the putamen of one side.

Paleostriatum. In the pallidum there was a definite decrease in the number of ganglion cells. The remaining cells were all diseased. They all stained lightly. The nucleus was shrunken and pyknotic, the cytoplasm was shrunken, the Nissl substance gone and there was an abundance of lipoid pigment in the cytoplasm. Shadow cells were occasionally seen; these were mere outline of cells. Calcium droplets were present throughout the tissue.

Thalamus. There were no changes in the thalamus. The ganglion cells were normal in appearance and number.

Substantia Nigra. The cells in both the Zona Compacta and Reticulata were normal in number. There was some depigmentation of the cells in this nucleus, but this was regarded as normal for this age.

Nucleus Ruber. No changes were seen either in the large or small ganglion cells.

Summary of Findings. The brain showed atrophy of the neostriatum, marked disease of the large ganglion cells of the caudate and putamen, less severe involvement of the small ganglion cells and moderate disease of the pallidal ganglion cells. The cortex showed nothing specific and the other basal ganglia were normal.

Comment. The necessity for reporting every case of spasmodic torticollis for which some cerebral lesion has been discovered is illustrated first by the few cases which have been studied with necropsy, and second by the fact that only by the accumulation of more and more evidence can we decide the truth of the controversy

concerning the basis of spasmodic torticollis. The time has not yet come for the taking of sides; insofar as the organic aspect of the problem is concerned we are still very much in the fact-gathering stage.

Report of Cases With Necropsy. The ablest and most strenuous proponent of the organic basis of spasmodic torticollis is Foerster,² who asserts that "spastic torticollis is a localized hyperkinetic condition limited to the neck muscles, which is due to an organic condition of the neostriatum." His evidence is based on the following facts: (1) Athetosis, generalized in the beginning, may disappear from the extremities and trunk and persist only in the neck muscles, giving a picture of torticollis. Foerster has seen this in cerebral diplegia, infantile hemiplegia and encephalitis. (2) Torticollis may for a varying period of time persist as a focal symptom and may later become part of a generalized athetosis. For Foerster, therefore, torticollis is a local athetosis which has its basis in a lesion in the neostriatum. He refuses to accept the emotional etiology of torticollis, and points out that during the World War there were thousands of all sorts of psychogenic reactions but very few cases of torticollis.

Foerster reports one of the few cases of torticollis with necropsy. He found *état criblé* throughout the substantia innominata, the nucleus lentiformis, claustrum and some of the adjacent convolutions of the insula. The putamen was especially affected, both the large and small ganglion cells being diseased. Many of the vessels had thickened adventitial coats. Many of the vessels showed perivascular infiltration with lymphocytes. Foerster regarded the focal lesion in the putamen as responsible for the neck spasm in his case.

One of the first necropsy studies in spasmodic torticollis was made by Bielschowsky in a case reported by Cassirer.¹ This was a man aged 29 who had had marked spasmodic spasm of the neck muscles for over two decades. There were also spasms involving the legs, arms and trunk. The clinical diagnosis was dystonia musculorum progressiva or torsion spasm. The patient died after an operation for relief of the torticollis. Bielschowsky found many ganglion cell shadows in the caudate and putamen, indicating subacute cell destruction. The larger cells of the neostriatum showed neuronophagia. Fatty degeneration was frequently seen. There were many *gitter* cells in the perivascular spaces. Similar changes but to a lesser degree were found in the thalamus. There were, therefore, changes in the putamen and caudate and to a lesser degree in the thalamus.

Wimmer⁴ reports a woman, aged 23, with tonic spasms of the neck, fingers, face and tongue in whom necropsy revealed marked microgyria of both frontal poles, a relative dysplasia of the right cerebral hemisphere, a large cyst extending from the right frontal pole to the inferior part of the right parietal lobe, a complete

absence of the caudate nucleus in the anterior part of the right cerebral hemisphere, and a marked atrophy of the right lenticular nucleus. Microscopic study revealed a marked loss of cells in the lenticular nucleus of the right side, the remaining cells showing atrophy, pyknosis and other evidences of disease. In this case, therefore, there were besides evidences of cerebral dysplasia, signs of neostriatal lesions on the right side.

More recently, Grinker and Walker³ report a case of spasmodic torticollis in a woman, aged 25, who had suffered with the disorder for 4 years, and who died of respiratory failure during a posterior root resection for the relief of her torticollis. Necropsy revealed fibrosis of the meninges, with a moderate loss of cortical ganglion cells, moderate chronic ganglion cell changes, scattered perivascular infiltration with round cells in the cortex and an increase of glial cells with many regressive forms present. The basal ganglia revealed the following findings: Pallor and pigment deposit in the ganglion cells of the thalamus, with moderate perivascular infiltration. Poor staining qualities of the ganglion cells of the caudate and putamen, and many areas of perivascular infiltration. The cells of the molecular layer of the cerebellum were greatly reduced in number, the Purkinje cells were reduced by half and there was pallor of the cells of the dentate nucleus. The cells of the substantia nigra were normal save for an occasional depigmented cell. Grinker felt that the process in his case was due to a chronic encephalitis characterized chiefly by hyperplasia of the meninges, perivascular round-cell infiltrations throughout the brain, chronic ganglion cell changes in the cortex and basal ganglia and cell loss in the cerebellum. He was unable to localize the lesion which was responsible for the torticollis because of the diffuse nature of the lesion, but he felt that the case added "one link to the chain of evidence suggesting that certain cases of spasmodic torticollis have an organic substratum."

Summary of Necropsy Findings. There are with our case only 5 cases of spasmodic torticollis with necropsy studies. Of these, 3 show unequivocal neostriatal lesions (Foerster, Cassirer, Alpers and Drayer). In the case of Grinker and Walker there was also involvement of the neostriatum, but there was in addition marked involvement of the cerebellum, and lesser involvement of the cerebral cortex and thalamus. In Wimmer's case only the right caudate, putamen and pallidum were affected, but there was in addition severe destruction of the right cerebral hemisphere from the frontal to the parietal lobes and other evidences of cerebral dysplasia. In the case of Alpers and Drayer there was destruction not only of the caudate and putamen, but to a lesser degree of the pallidum.

While either a pure or a predominant neostriatal lesion was present in 3 cases, and while in the 2 other cases the neostriatum was affected, there were in the latter sufficiently widespread involve-

ment of other parts of the brain to throw some doubt on the purely striatal localization of the lesion in these cases of spasmodic torticollis. The significance of these other findings is not clear. For that matter, the significance of the striatal change is not clear in explaining the pathogenesis of the movements of torticollis. In any event, it is fair to state that the striatal changes are common to all the 5 cases reported. However, the other findings cannot be disregarded. They would appear to be of less value than the neo-striatal findings because of the 3 more or less pure cases of striatal lesions with pictures of true torticollis and with no involvement of the cerebrum or cerebellum.

The few cases with necropsy studies should not occasion too great surprise, since torticollis is not a cause of death. These patients live for many years, probably disappear from observation and do not die in hospitals where, of course, necropsy studies are most likely to be performed. Of the 5 cases reported, 2 have died during operations for relief of the torticollis.

Significance of the Necropsy Findings. If we assume that spasmodic torticollis is an athetoid movement, and that choreo-athetosis is due to lesions in the neostriatum, then the findings in the latter have definite significance. They certainly cannot be disregarded. The question arises then how it is that a focal movement of the neck muscles is produced by cell disease in the neostriatum. The answer to this is given in part by the investigations of C. and O. Vogt, who showed that there is in the striatum and pallidum a rough sort of localization which corresponds to that found in the cerebral cortex. It is difficult nevertheless to reconcile those cases of torticollis with complete destruction of the neostriatal cells.

In our present state of knowledge it is possible only to state that in some cases of spasmodic torticollis there is an organic basis, that this basis is either partial or complete destruction of the neostriatum, and that its significance for the pathogenesis of the torticollis is not yet clear. This must depend on the recording of further cases which may help to clarify the problem.

Conclusions. 1. A case of spasmodic torticollis with necropsy findings is recorded. These consisted of destruction of the large cells of the caudate and putamen, and less damage to the smaller cells and to the cells of the pallidum.

2. Four other cases of spasmodic torticollis with necropsy studies are reported from the literature.

3. The conclusion is reached that in some cases of spasmodic torticollis there is an organic basis.

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**PITUITRIN INJECTIONS AND THE BLOOD PICTURE IN THE
NORMAL AND HYPOPHYSECTOMIZED GUINEA-PIG.**

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IN his recent review of the endocrines in blood disorders, Hubble,⁴ referring to the anemia of Simmonds' disease and of Fröhlich's syndrome, comments on the dearth of experimental evidence for or against some essential rôle for the pituitary gland in hematopoiesis. Collip¹ mentions obtaining evidence suggestive of an effect of pituitary extracts rich in the adrenotropic hormone on the blood-forming organs, and Houssay³ has observed a slightly subnormal hemoglobin content of the blood of hypophysectomized rabbits. Dodds and Noble² have shown that the gastric dysfunction resulting from the injection of massive doses of pituitrin into experimental animals is accompanied by a severe macrocytic anemia from which the animals spontaneously recover. Control extracts of other tissues were shown to have no such adverse effect.

In this paper are recorded the hematologic findings on guinea-pigs deprived of the pituitary gland. The effect of injecting relatively large doses of pituitrin into these and into normal animals has also been observed.

Experimental. For the operation active, healthy guinea-pigs of about 500 to 600 gm. were chosen. Both males and females were used. They received no special care other than being well fed and comfortably housed. The pituitary operation was carried out by one of us (M. K. McP.) according to the method described by McPhail and Parkes.⁶ Some difficulty was first experienced in keeping the animals alive after the operation, a large percentage dying of bronchopneumonia. This difficulty was ultimately overcome by speeding up the operation so that the duration of ether anesthesia was made as short as possible. The improvement in survival as a result of this simple change in technique was quite remarkable, and very few animals were now lost. It was only after the success of the operation was assured, that is, when 2 weeks after the operation the animals appeared active and healthy, and had not suffered an excessive loss of weight, that the blood studies were begun. Blood was obtained from the ear lobe. The hypophysectomized animal bleeds remarkably freely compared with the intact animal, but the blood clots readily. Excessive bleeding was carefully guarded against. Hemoglobin determinations were made with a Sahli hemoglobinometer which had been standardized by oxygen-combining capacity measurements made by the Van Slyke technique. The reticulocyte counts were made by the procedure outlined by Jacobson.⁵

The pituitrin employed was a Parke, Davis & Co. product containing 10 pressor and 10 oxytocic units per cc. and was injected either subcutane-

ously or intraperitoneally. In preliminary experiments hypophysectomized and normal animals were injected with 5 cc. of pituitrin. Extreme shock, with the majority dying in a comatose state, was the result. In subsequent experiments, when the single injection never exceeded 3 cc., only one fatality occurred.

At postmortem a careful check was made of the success of the operation. In addition the upper portion of the alimentary tract was examined macroscopically. In all cases the fundus portion of the stomach was sectioned and a microscopic examination made.

TABLE 1.—HYPOPHYSECTOMIZED GUINEA-PIGS.

Days postoperative.	Guinea-pig. No. 101. ♂562 gm.				Guinea-pig. No. 115. ♀525 gm.			
	R. B. C. (millions).	Hemoglobin (gm. 100 cc.).	Reticulocytes (per cent).	Body weight (gm.).	Days postoper.	R. B. C. (millions).	Hemoglobin (gm. 100 cc.).	Body weight (gm.).
(Normal average*)	5.70	13.8	3.0					
7	5.75	12.0	1.1	..	7	4.68	11.8	1.3
14	5.10	11.3	1.1	..	10	5.09	..	2.1
22	5.25	11.1	1.9	..	13	5.58	10.7	1.7
30	4.84	12.3	1.5	510	22	5.86	11.3	1.7
35	4.97	12.1	2.3	..	28	5.02	11.1	1.9
44	5.11	11.5	1.7	490	39	4.98	10.3	..
50	4.56	11.4	1.7					515
62	4.15	11.5	2.2	471				517

Postmortem Notes: Hypophysectomy complete, testes small and flabby. Seminal vesicles still quite large.

Postmortem: Hypophysectomy complete.

* According to Scarborough, R. A., Yale J. Biol. and Med., 3, 63, 169, 1930; 3, 267, 359, 431, 547, 1931; 4, 69, 1931.

Discussion of Results. In Table 1 the blood findings with hypophysectomized guinea-pigs over a period of 1 to 2 months are given. These results are representative of the data obtained with a number of other pigs not included in the table, and show when compared with the levels for intact guinea-pigs of which the initial values in Table 2 are typical that removal of the pituitary gland exerts very little, if any effect on the red-cell count and hemoglobin content of the blood.

The injection of pituitrin into intact guinea-pigs in amounts of the order of 5 to 10 cc. per kg. body weight produces an anemia of varying degree of severity (Table 2). In these experiments the injection of this pituitary extract was followed in a day or two by a hardening of the abdominal wall. The necrosis in some cases was confined to a small area at the site of injection, while in other animals it was more profuse. In some animals the condition did not occur. In the case of guinea-pigs Nos. 80 and 81, particular care was taken to inject the pituitrin extremely slowly into the peritoneal cavity, taking at least 5 minutes to administer the dose. In 1 case a severe necrosis resulted, while the other animal was not affected. It was observed that in these experiments in general the severity and duration of the anemia and the magnitude of the reticulocytosis was greatest in those animals in which the necrosis and sloughing was

most extensive. This was particularly indicated in the results (Table 3) of injecting pituitrin into the hypophysectomized animals. Since the onset of the anemia came somewhat later than Dodds and Noble found, we have tried the injection of larger amounts of pituitrin, given in repeated small doses. The results shown in Table 4 were not significantly different from the previous ones.

TABLE 2.—NORMAL GUINEA-PIGS (PITUITRIN INJECTED).

	No. 70 ♂ 529 gm.			No. 63 ♂ 536 gm.			No. 80 ♀ 354 gm.			No. 81 ♀ 367 gm.		
	R. B. C.	Hb.	Retic.	R. B. C.	Hb.	Retic.	R. B. C.	Hb.	Retic.	R. B. C.	Hb.	Retic.
Day of injection (injected 3 cc. pituitrin)	5 24	12 3	0.9	5 07	11.6	1.8	5.10	11.0	1.0	4.49	10.9	1 5
Days after injection												
2	6.65	13.5	1.0	5.72	11.8	1.2	4.86	10.7	2.1	4.51	10.5	1.9
4	5.11	10.5	1.7	4.85	9.8	1.3	4.39	9.7	2.6	4.48	9.7	2.5
6	4.71	10.7	1.4	4.56	8.6	1.4	4.81	8.8	3.8	4.14	10.3	2.1
8	4.15	8.2	2.1	4.68	8.2	1.4	1.93	8.8	6.9	1.88	8.6	7.6
11	3.84	9.3	5.8	4.08	8.8	5.9	2.18	8.6	9.4	2.00	..	8.9
13	3.25	8.4	23.8	3.19	6.8	18.7	2.05	9.1	10.3	2.10	8.8	9.0
15	4.95	10.5	15.0	1.93	7.7	31.2	2.10	9.8	7.2	1.14	8.8	11.0
17	4.89	11.6	7.1	1.99	7.3	30.0	2.14	9.0	6.4	1.48	6.7	19.9
18	4.87	11.6	5.2	2.51	8.0	19.0	4.29	9.5	5.4	1.26	6.6	10.5
20	3.40	9.3	7.9	4.71	9.9	4.4	2.74	6.3	8.0
Condition of abdominal wall.	Induration—no wound.			Profuse necrosis—large wound with sloughing.			No induration or necrosis.			Necrosis—sloughing		
Body weight at end of experiment (gm.)	435			445			348			375		

TABLE 3.—HYPOPHYSECTOMIZED GUINEA-PIGS. PITUITRIN—SINGLE INJECTION.

Time from operation.	No. 104 ♀ 600 gm.			No. 105 ♀ 546 gm.			No. 120 ♀ 565 gm.		
	16 days.			16 days.			14 days.		
	R. B. C.	Hb.	Retic.	R. B. C.	Hb.	Retic.	R. B. C.	Hb.	Retic.
Day of injection (injected 3 cc. pituitrin)	4.96	11.0	1.4	5.64	12.3	1.8	5.11	10.9	1.0
Days after injection.									
2	4.86	9.8	1.4	5.90	10.9	1.9	4.80	10.1	1.4
4	4.48	9.8	1.7	5.58	10.2	1.7	3.91	9.8	2.8
6	4.00	7.7	1.4	4.37	10.0	2.1	3.83	9.2	3.8
9	3.57	7.5	13.0	3.26	8.9	14.4	2.38	8.9	6.0
11	2.58	5.6	39.3	3.67	9.3	21.2	2.91	8.1	14.6
13	1.90	5.7	31.0	1.28	9.3	10.7	2.41	7.3	15.0
15	0.68	2.9	34.0	3.50	8.4	6.0	2.92	8.0	10.2
18	0.81	3.0	39.0	3.48	9.5	3.4	1.96	7.1	7.9
Weight at completion of experiment (gm.)	465			440			465		
Condition of abdominal wall—	Profuse necrosis large wound with sloughing.			No induration—no necrosis.			Necrosis—large wound—sloughing.		
Postmortem Notes:	Hypophysectomy incomplete. Left half of anterior-lobe in place, but paler than normal. Uterus pale and large.			Hypophysectomy complete—pituitary fossa clean. Ovaries small—uterus large.			Hypophysectomy complete.		

TABLE 4.—HYPOPHYSECTOMIZED GUINEA-PIGS; PITUITRIN (REPEATED INJECTIONS).

Time from operation.	No. 135 ♀ 489 gm.			No. 124 ♀ 582 gm.			No. 126 ♀ 535 gm.		
	15 days.			14 days.			14 days.		
	R. B. C.	Hb.	Retic.	R. B. C.	Hb.	Retic.	R. B. C.	Hb.	Retic.
Day of 1st injection of 1 cc. pituitrin	5.50	10.9	1.3	5.13	10.5	1.8	4.95	11.1	2.0
Days after 1st injection									
1 (2d injection, 2 cc. pituitrin).	5.12	11.0	1.6	5.13	10.2	1.1	4.88	9.3	1.8
2 (3d injection, 2 cc. pituitrin)	4.51	9.7	1.0	4.77	11.3	1.0	3.04	9.6	1.9
3 (4th injection, 2 cc. pituitrin)	3.55	8.8	2.3	4.58	9.7	1.9	2.76	8.7	3.4
4	2.57	8.6	22.7	3.00	9.7	2.0	2.39	8.0	5.6
6	2.75	7.4	21.7	1.87	8.6	22.0	2.63	8.7	18.0
8	3.0	7.4	13.2	3.04	8.4	16.0	1.38	9.2	22.0
10	3.67	8.1	8.0	3.10	9.2	10.6	...	9.8	14.4
12	3.20	9.2	11.0	3.46	8.1	8.1	1.70	9.8	8.3
14	3.51	9.9	9.0	2.75	8.8	6.1	2.41	9.3	9.1
16									
17									
Weight at completion of experiment (gm.)	465			440			465		
Condition of abdominal wall—induration—no necrosis.				Induration—no necrosis			Extensive necrosis and sloughing.		
Postmortem Notes: Hypophysectomy complete.				Hypophysectomy complete.			Possible that fragment of anterior lobe not removed. Uterus and ovaries small.		

Macroscopic and microscopic examination of the stomach of every animal (Dr. J. W. MacGregor) showed that, in all cases, the stomach appeared normal, there being no ulceration. The mucosa was perfectly intact and showed no scarring. While it is still possible that an inflammatory condition had been present and that the animals had recovered before autopsy, there was no evidence that there had been any acute perforative lesions of the fundus region of the stomach.

Selye, Stehle and Collip⁷ have confirmed the fact that the injection of pituitrin can produce severe hemorrhagic lesions of the acid-bearing region of the stomach and have shown further that the pressor principle is responsible for this effect. If in our experiments such lesions had not occurred, as appears to be the case, it may be that the number of pressor units injected was too small or that the material was poorly absorbed. Whatever the explanation, it is particularly significant that, nevertheless, a severe anemia did develop and that several of the animals were still extremely anemic at the time of the autopsy.

In general, nothing suggestive of a hormonal connection between the pituitary gland, gastric function and blood formation has come out of these experiments.

Summary. 1. Hypophysectomy of the guinea-pig did not result in any marked change in the red-cell and hemoglobin content of the blood.

2. The injection of relatively large doses of commercial pituitrin into normal and hypophysectomized guinea-pigs was followed.

after a rather prolonged period, by the development of a severe anemia.

3. The postmortem examination of these guinea-pigs, some of which were still markedly anemic, did not show any occurrence of acute gastric lesions. Microscopic examination of sections of the fundus failed to reveal any indications that ulceration had occurred.

For much special assistance we have to thank Dr. J. W. MacGregor (Assistant Provincial Pathologist) and Dr. M. M. Cantor (of the Department of Biochemistry). We wish to record our thanks to Messrs. Parke, Davis & Co. who have generously placed pituitrin at our disposal. To the Carnegie Research Grant committee of the University we are indebted for a grant for expenses.

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RECURRENCE IN MIXED TUMORS OF THE SOFT PALATE.

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RECURRENCE in mixed tumors of the soft palate is extremely rare for the following two reasons: First, although it has been generally assumed that these tumors are analogous in all ways to mixed tumors in the parotid, the literature shows that they differ from the corresponding parotid tumors in that recurrence is unusual. Furthermore only 60 mixed tumors of the soft palate have been reported. Beck¹ reported a case that recurred 3 weeks after surgical removal, and within 5 weeks was the size of the original tumor. In a discussion of mixed tumors of the palate, Patey^{2a} referred to a case with recurrence after 2 years. He failed to mention whether the tumor originated in the hard or soft palate. Duany³ recorded a recurrence confirmed by biopsy 7½ years after electrocoagulation of the original tumor. At the time of the report 4 month later, the lesion had been reduced in size though not cured by radium therapy.

The following case was originally reported by Dr. Robert Ivy;^{4a,b} it is presented again because of a very late recurrence.

Case Report. The patient, a white woman, aged 52, was readmitted to this hospital on the service of Dr. Alfred Stengel, August 21, 1935. She had two groups of symptoms with no apparent relation between them. Her major complaints were a burning pain in the right lower quadrant and legs, and a lump in the palate. The former had begun 6 months before and as it was associated with absence of the patellar and Achilles reflexes, with wasting and weakness of the legs, and with diminished vibratory sensation, it was thought to be a neuritis secondary to diabetes mellitus which had been discovered a few weeks before admission.

The history of the tumor in the palate was of much longer duration. About 21 years previously a tumor had appeared in the left side of the soft palate. Excised in February, 1914, it was diagnosed mixed tumor. The patient experienced no further trouble until about 1925, when she noticed another small swelling in the same location. Since 1925, the lesion gradually but steadily enlarged to the size of a pecan nut. The only symptom was a constant awareness of the tumor. The patient had experienced no pain and no difficulty in swallowing, breathing, or talking.

The tumor was situated slightly to the left of the midline and was approximately 2 cm. in its anteroposterior diameter and slightly less in the other diameters. It was firm, smoothly covered with mucous membrane and not tender. It was movable but moved more readily near the free border of the palate than anteriorly where it was splinted by the hard palate.

On August 31, 1935, the patient was transferred to the surgical service of Dr. I. S. Ravdin. On that date, using infiltration anesthesia, the tumor was excised. It was circumscribed by a friable capsule which was quite definite on the buccal side but seemed less distinct on the nasal side. The capsule broke before excision was completed. The interior of the tumor was composed of whitish material that crumbled readily without bleeding. This was removed and the remainder of the capsule dissected out. The wound was closed without drainage but separated on the 5th postoperative day and healed secondarily. The patient was discharged on the 14th postoperative day and returned for postoperative irradiation 2 weeks later. At this time healing was complete. The patient reported after 11 months that she had no evidence of recurrence.

Pathologic Report. Grossly, the specimen consisted of several pieces of tissue removed from the soft palate. Together they measured about 2 cm. in diameter. The tissue was pale and soft. It was not possible to identify the complete capsule.

Microscopically, the tumor varied greatly in different sections. Some areas were dominantly angiomatous with an abundant fibrous stroma in which there were occasional collections of fatty tissue. Other areas showed imperfectly formed acini filled with mucoid material (Fig. 1). There was one small area that had an adenomatous character. The acini were lined with a single layer of cylindrical cells (Fig. 2). Other sections showed epithelial hyperplasia which had a medullary character. The cells were large and pale and had vesicular nuclei. The solid areas had a fibrillar myxomatous ground substance and contained numerous cylindrical hyaline masses around which there were no acinar formations (Fig. 3). The findings were not unlike those seen in mixed tumor of the parotid. There was, however, more evidence of cellular proliferation than is usually seen in tumors located in the parotid. The predominating tissue was of the spindle-cell type.

Diagnosis. Mixed tumor of cylindromatous type.

Discussion. Mixed tumors of the soft palate are comparatively rare. Sonnenschein¹², in 1929, analyzed Eggers' 92 cases of mixed tumor of both the hard and soft palate and found that "well under

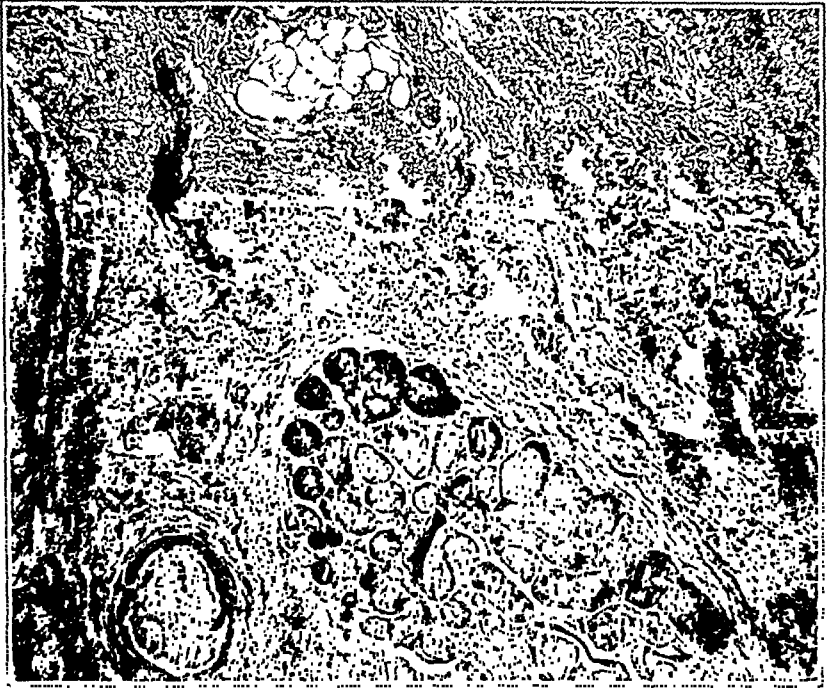


FIG. 1.—Photomicrograph demonstrating angiomatous and adipose tissue with a collection of acini filled with mucoid material. (Low power.)



FIG. 2.—Photomicrograph showing an area of adenomatous tissue bordering on the predominant spindle-cell tissue found throughout the tumor. (Low power.)

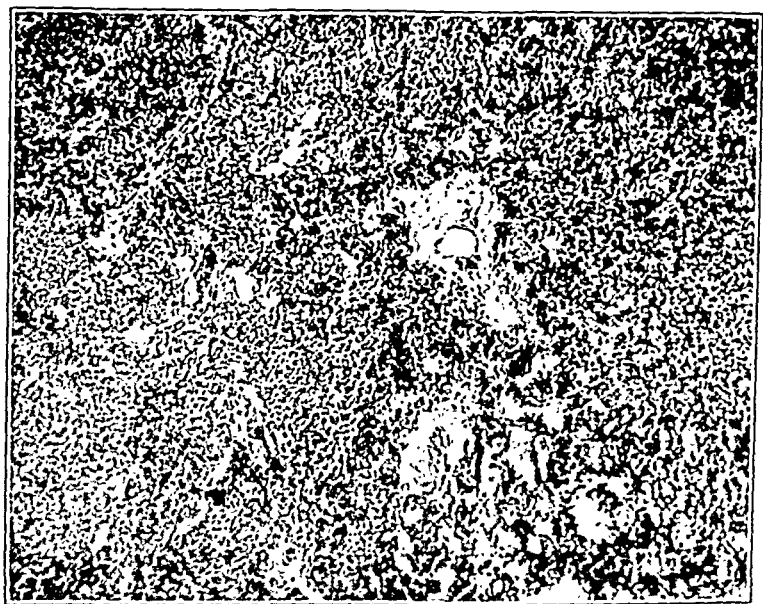


FIG. 3.—Photomicrograph showing epithelial hyperplasia with cylindromatous formations. (Low power.)

fifty" were of the soft palate. Failure of many of the reports accurately to locate the lesion, and the occasional tumor which seems to involve both the hard and soft palate (di Lorenzo's¹² case), account for the inability to state with accuracy the exact number located in the soft palate. In the latter region 12 new cases have been reported since Sonnenschein's article in 1929 (Table 1).

TABLE 1.—CASES OF MIXED TUMOR OF THE SOFT PALATE REPORTED SINCE 1928.

	Age.	Sex.	Side.	Duration.	Encapsulation.
Beck ¹	27	M	Right	7	No
Soubiron and Bianchi ¹⁷	43	M	..	3	Yes
Duany ⁵	30	F	Left	8	
Blumberg and Terry ²	35	M	Right	..	Yes
Holmgren ⁹	24	F	Right	1	Yes
	51	F	Left	8	Yes
	27	F	Left	12	Yes
Carruthers ³	48	F	Left	1	Yes
Heitz ⁸	43	M	Right	11	Yes
Jarman ¹¹	17	M	Center	Noted in routine Px	Yes
Davis ⁴	27	F	Right	2	
	22	F	Left	6	

The recurrence shown in the case here presented makes it unusual. The interval of 11 years between removal and recurrence is the longest period on record. The slow growth of the recurrence is notable, the tumor requiring 10 years of gradual growth to attain the size of a pecan nut. Microscopically, the original and the recurrent tumors resemble each other closely. Ivy's description is applicable to the tumor here presented. To quote, "Microscopic examination shows a strain of pink staining homogeneous substance and large oval-shaped cells with vesicular nuclei taking a deep hematoxylin stain." (Cp. Fig. 3.) "These cells in some places were arranged in the form of alveoli . . ." (Cp. Fig. 2.) "In other situations the cells formed irregular extensions through the stroma with no basement membrane or line of demarcation of any kind." (Cp. Fig. 3.)

It is difficult to compare the types of mixed tumor found in the reported recurrences because of the inadequate descriptions. Patey simply stated there was a recurrence of the original tumor. From Duany's description it appears as if the tumor which he reported might have been a cylindroma. Beck classed the original tumor in his case as a myxo-fibro-chondroma. The description of the recurrence likewise fits this designation.

Three theories have been advanced to explain recurrence in these tumors. Sonnenschein believes that they are seedlings caused by a rupture of the capsule in the removal of the original tumor. Beck is convinced that in his case recurrence arose from the "remains of the capsule." Erich,¹⁶ in his paper on mixed tumors of the salivary glands, believes that these tumors might in some cases be sister

tumors arising from two misplaced blastomeres which start growth at different times. In the case here presented the history of the tumor being "easily shelled out" in 1914, and the 11-year interval between the removal and the first evidence of recurrence, seem to be strong arguments against this tumor having arisen from a seeding or from the "remains of the capsule." Yet the location of both tumors in the same region and the almost identical histopathology seem to point to this method of recurrence. There is the possibility that 2 misplaced blastomeres might have started growth at different times activated by unknown factors which continued to operate after the removal of the original tumor.

Whatever the mechanism of recurrence may be, most authors are agreed that it is more prone to occur in cases in which the capsule is incomplete or is broken during removal.

Treatment. Review of the literature shows that in a majority of cases surgical excision was comparatively easy. Where the tumors were completely encapsulated the dissection was not difficult, hemorrhage was slight, and primary union the rule. The success of this treatment is attested by the low incidence of recurrence.

Thus far too few cases have been treated with irradiation to permit any estimate of its efficacy. However, irradiation has been used in the treatment of the closely related mixed tumors in the salivary glands. At this hospital experience with radiation therapy in this latter group of tumors was in agreement with the findings of Sistrunk,¹⁵ namely, that it usually caused very little regression. In contrast, it must be noted that some writers have observed a marked reduction in these growths following irradiation, occasionally to the extent that they are reduced to inert hyaline masses.¹⁹ Bland-Sutton (quoted by Patey¹³), Stewart,¹⁸ and others have found that interstitial irradiation gave the best results. In the case here presented the clinician, the pathologist and the radiologist agreed that postoperative irradiation should be administered in the hope of destroying any remaining elements that might have been retained. Accordingly the patient was given a total of 655 mg. hours of irradiation by radium pack. A moulded plaque was placed in the mouth separated from the lesion by a 2-mm. platinum filter.

Quick¹⁴ has suggested biopsy in mixed tumors of the parotid to determine whether or not they may be of a cellular type and therefore amenable to irradiation. Duany performed a biopsy of the recurrent tumor in his case. It is our belief that the procedure is dangerous in this group of tumors regardless of location; for we feel confident that any encapsulated embryonal tumor subjected to partial open mutilation may be stimulated to active growth.

Summary. 1. A case of recurrent mixed tumor of the soft palate is presented.

2. Twelve cases of mixed tumor of the soft palate have been found in the literature since Sonnenschein's report in 1929.

3. Recurrence has been noted in 3 previously reported cases.
4. The treatment of choice is surgical excision followed by irradiation if complete extracapsular removal is not accomplished.

The writers are indebted to Drs. Stengel and Ravdin for permission to present the case; to Dr. Joseph McFarland for reviewing the slides; and to Dr. A. E. Bothe for valuable suggestions in preparation of the paper.

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CARBAMINOYLCHOLINE—(DORYL OR LENTIN). ITS ACTION ON NORMAL PERSONS, IN PERIPHERAL VASCULAR DISEASE, AND IN CERTAIN OTHER CLINICAL CONDITIONS.

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CARBAMINOYLCHOLINE chloride ($\text{NH}_2\text{COOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_3\text{Cl}$) (trade names Doryl and Lentin) was synthesized by Kreitmair⁷ in 1932. Its action in animals has been carefully studied, especially by Kreitmair, Noll,⁸ Dautrebande,^{1,2a} and Simonart.¹³ The drug is stable, and powerful effects are obtained by extremely minute dosage. Its action resembles that of many other choline derivatives, producing effects similar to those which follow stimulation of parasympathetic nerves. Accordingly increased sweating and salivation; cardiac slowing; increased intestinal, uterine, and vesical activity; and general vasodilatation with resulting diminution of blood pressure, are conspicuous after its administration to animal preparations. In addition carbaminoylcholine has an energetic nicotine-like action on ganglion cells and striated muscle, in which respect it resembles acetylcholine and differs from acetyl- β -methylcholine. Atropine antagonizes the parasympathetic action but not the nicotine-like effects.

Judged by the effective dosage for man carbaminoylcholine is the most powerful choline derivative known. It is also the most toxic

for animals. The ratio of the subcutaneous therapeutic dose for man to the subcutaneous toxic dose in rats is about the same for carbaminoylcholine as for acetyl- β -methylcholine.*

Under the trade name of lentin, the drug has been widely used in veterinary medicine in Germany for the treatment of gastrointestinal conditions in animals.⁵

The first clinical investigation was made by Dautrebande and Marechal^{2b} in 1933. In their cases, some with and some without hypertension, a slow intravenous injection of 0.1 mg. produced no disagreeable symptoms and was followed in about 30 seconds by a diminution of blood pressure of 50 to 100 mm. Hg., the previous level being regained within 5 or 10 minutes. Vasodilatation, a sensation of warmth, increased sounds of intestinal movement, salivation, and lachrymation, almost always accompanied the action. The subcutaneous administration of 0.2 to 0.3 mg. was followed by a more prolonged fall of blood pressure lasting 20 to 40 minutes. These authors detected no fall of blood pressure after oral or rectal administration. Our results are very similar. Since the brief report of Dautrebande and Marechal several short articles have appeared giving favorable reports of the use of this drug in postoperative urinary retention,^{11b} eclampsia,^{11a,8} ozema,⁴ increased ocular tension,¹⁶ and by means of electrophoresis.^{13,6}

We first administered the drug† in increasing dosage to 26 normal young adult volunteers. With this experience behind us we employed it in the treatment of disease conditions which its action seemed adapted to benefit. The drug causes striking relief of pain in certain cases of peripheral vascular disease.

Methods of Administration. Not being hygroscopic the drug can be administered conveniently in hypodermic tablets or tablet triturates of 0.2 and 0.4 mg. Occasionally patients complain of pain at the site of subcutaneous injection. This can usually be avoided by injecting the dissolved tablets in not less than 1 cc. of water.

We have not attempted intravenous administration, thinking it unnecessary and more hazardous. That it is a feasible method has been demonstrated.^{2b}

General Effects. *The Action after Subcutaneous Administration. On Normal Persons.* Twenty-six healthy medical students served as volunteer subjects. The routine observations were made by myself, by Dr. William Test, or by students under our supervision. The subjects lay upon a couch for a preliminary rest period of at least 15 minutes and remained there for the duration of the observations. Dosage ranged from 0.1 to 1.0 mg. subcutaneously; from 0.4 to 1.0 mg. orally. The effects are summarized in Table I.

* I am indebted to Dr. H. Molitor for permission to examine and use his data on the toxicity of various choline derivatives for animals.

† All the choline derivatives used were supplied through the kindness of Merrick & Co., Inc., Rahway, N. J.

TABLE 1.—ACTION OF CARBAMINOYLCHOLINE CHLORIDE ON NORMAL PERSONS.

	Subcutaneous dosage.			Oral dosage.	
	0.1 to 0.3 mg.	0.4 to 0.6 mg.	0.7 to 1.0 mg.	0.4 to 0.6 mg.	0.8 to 1.0 mg.
Number of cases in each group . . .	5	7	3	4	3
Number of cases showing effects, given below					
Systolic blood pressure, mm. Hg:					
Change less than 5	2	4	2	1	3
Fall 5-10	2	2	1	3	
Rise 5-10	1	2			
Pulse rate:					
Change less than 5	2	4	1	2	1
Increase 5-10	3	1	1		
Increase 10-15		1	1		
Increase over 15		1			
Decrease 5-10				1	1
Decrease more than 10				1	1
Flush	3	7	3	2	2
Sensation of warmth	4	6	2	1	
Later sensation of cold		4	2		
Sweating	2	7	3	1	1
Salivation	3	6	2	..	1
Lachrymation		2	2		
Increased peristalsis	2	7	2	2	
Abdominal cramps		5	1	..	1
Epigastric discomfort		1	1	..	4
Pain in bladder or urethra		1			
Desire to void		2	2		
Belching		1	1
Headache	1	2

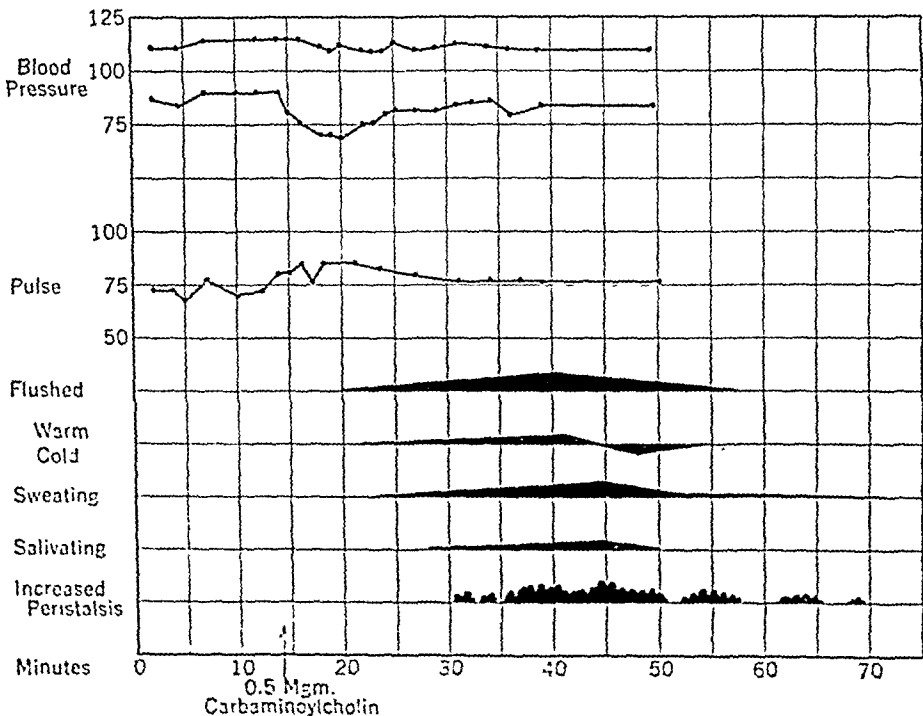


FIG. 1.—Action of 0.5 mg. carbaminoylcholine given subcutaneously to a normal subject.

A typical effect after a dose of 0.5 mg. is shown in Fig. 1. After this dosage no drug effect was noted by the subject for from 6 to 10 minutes after the injection. The action then came on very gradually. Flushing of the face, accompanied by a sensation of warmth was noted first. Slight perspiration appeared some minutes later accompanied by such slight salivation that it was not observed by some. About 15 minutes after the injection increased peristalsis was usually noted by the subject and borborygmi soon became audible to the observers, often without a stethoscope. The height of the action appeared 20 to 30 minutes after the injection when sweating was generalized, the subject very conscious of the sensation of heat in his ears and face, and of rumbling in his abdomen with occasional cramps. Some had a desire to urinate at this time. These effects passed off gradually and were scarcely noticeable an hour after the injection.

Changes in blood pressure and pulse rate were so slight that the subject was usually unaware of them. Soon after the injection a slight increase in pulse rate and a small fall of diastolic blood pressure were often, but not always, seen. Palpitation was seldom noted. Slight lachrymation was seen occasionally. One subject was conscious of difficulty with visual accommodation. No effect on respiration was obvious.

After larger dosage, as 1 mg., the drug's action still came on slowly and gradually. There was usually no more effect on pulse and blood pressure than is shown in Fig. 1, but all the other effects were more intense and, about 25 minutes after the injection, the subjects became so uncomfortable from abdominal cramps that atropine was given in every instance.

Small doses, such as 0.1 mg., caused flushing and slight sweating without any other observed effects.

On Patients the general effects were the same as on normal persons. After repeated injections cumulation became manifest. More than one patient, placed on 0.4 mg. t.i.d. for 3 days or longer, insisted that we were increasing the dose. Daily dosage repeated for a period of 10 days or longer did not cause any noteworthy change in the level of pulse rate or blood pressure recorded on the hospital chart.

Action After Oral Administration. On 6 normal persons doses of less than 0.6 mg. caused the very slight effects mentioned in Table 1.

The experience of the author seems typical of that of the others. One hour after taking 0.6 mg. he noted slight sweating of the palms and a very slight gastric sensation with belching. An hour later he felt a transient sensation of tightness in the bladder, and, still later, an unusual sensation in the eyes, perhaps due to stimulation of accommodation. Pulse rate was essentially unaltered, the systolic blood pressure diminished about 10 mm. All the effects were so slight that they were difficult to describe and there was some doubt whether they should have been attributed to the drug.

The drug has been given orally to over 25 *patients*. The great majority tolerated from 0.2 to 0.4 mg. once or twice a day. But several were unable to take 0.4 mg. In 2 this dose caused marked nausea and malaise. Two others complained of excessive sweating.

In contrast to this, 1 patient with peripheral vascular disease took 2 mg. at one dose without any discomfort after it. Another, with spastic obstruction of the lower esophagus, the passage of food being delayed temporarily but complete eventually, took 1.6 mg. t.i.d. by mouth for 14 days without the production of any uncomfortable symptoms at all.

The cumulative effect of the drug was marked. Four patients took from 0.2 to 0.4 mg. daily from 1 to 3 weeks without discomfort, but eventually the same amount produced so much more action that the dosage had to be reduced.

It is obvious, therefore, that carbaminoylcholine gives irregular effects after oral administration, so that a dose giving disagreeable symptoms in some may be well tolerated by others.

Twice daily administration of the drug for 3 and 8 weeks, to 2 patients, in the largest dose that produced no uncomfortable manifestations, did not cause any noteworthy alteration in the general level of pulse rate or blood pressure; nor did it cause an increased number of stools.

Special Studies. In 6 cases, 5 of them with peripheral vascular disease and apparently benefited by the drug, a more elaborate study was undertaken which will be reported in detail in a subsequent publication.³ After an average dose of 0.5 mg. subcutaneously the average changes were as follows: *pulse rate* increased 7.6%; *mean blood pressure* diminished 6.2%; *basal metabolic rate* increased 3.5%; *basal cardiac output* increased 12.3%; *respiratory rate* was practically unchanged; *respiratory volume* per minute increased 5.6%. Of these the changes in blood pressure, pulse rate, and respiratory volume, were statistically significant (for $P = 0.05$) while the larger change of cardiac output, less constant than the other drug effects, missed significance by a narrow margin. The changes demonstrated are those common to drugs that primarily lower blood pressure.

Electrocardiograms, taken before and after the drug in the above 6 cases and in 2 normal persons, all with normal rhythm, showed nothing other than the changes of rate described before. One case of auricular fibrillation was given the drug in increasing doses, until the side effects became uncomfortable, without producing any noteworthy change in the electrocardiogram.

In 2 cases the fasting *blood sugar* and *blood urea nitrogen* were unchanged by the prolonged administration of the drug.*

Four cases of benign partial obstruction of the lower esophagus with pre-ventriculosis have been examined under the *fluoroscope* after a barium meal to study the drug's action. In the first case no

* I am indebted to Dr. W. F. Sunderman for these analyses.

barium had entered the stomach before the drug. Within 1 minute after 0.5 mg. had been given subcutaneously an increase in esophageal peristalsis was noted. Four minutes later this was striking and small amounts of barium were pushed into the stomach by the larger waves; 25 minutes later esophageal peristalsis was still much increased and most of the barium was in the stomach which could be seen to be hyperactive also. The other 3 cases, observed by Dr. G. D. Gammon, showed a very similar picture after 0.4 mg. subcutaneously. There was no marked relaxation of the cardia in any, but large waves were induced which forced small amounts of the barium into the stomach.

Two of these patients were given a course of the drug by mouth. In one there was no improvement in the patient's symptoms, in the other improvement could be attributed to the repeated dilations of the esophagus carried on simultaneously.

Studies of the effect of carbaminoylecholine on *skin temperature* have been made in 7 cases of peripheral vascular disease. The patients were all placed in a cool constant temperature room. Thermal junctions were attached to their fingers or toes by wide strips of adhesive.

A case of mild Raynaud's disease was placed in this room with hands exposed. The temperature of the ball of each finger fell rapidly till it reached within 1°C . of the air temperature, $18^{\circ} \pm 1^{\circ}\text{C}$. Increased pallor without cyanosis, accompanied this change. About 1 hour after the oral administration of 0.3 mg. carbaminoylecholine the temperature of the finger tips began to rise as flushing of the face was noted. The maximum increase was 6°C ., the minimum 4.2°C . All fingers had become a good red color when the experiment was terminated 2 hours after the administration of the drug.

The feet of 3 cases of diabetic peripheral vascular disease and 3 of thromboangiitis obliterans were tested similarly. Five of these cases, comfortable when tested, had formerly had rest pain in their feet partly or completely relieved by carbaminoylecholine, and were given the same dose which had previously relieved them. In only 2 patients was any evidence of vasodilatation in the feet secured. In 1 case of thromboangiitis the action following a dose of 1 mg. by mouth was accompanied by a reversal of the temperature trend in the feet, the temperature of the toes increasing between 1.8 and 1.4°C . Three days later an oral dose of 2 mg. gave substantially the same result. In 4 cases subcutaneous injections ranging from 0.4 to 0.8 mg. produced the usual drug effects not accompanied by any rise of skin temperature in the feet.

Ten cases of *hypertension* have received the drug. To test its acute effects the subjects remained in bed all day. In a case of diabetes with arteriosclerosis the blood pressure ranged from 208/90 to 190/93 during the 15-minute control period. Ten minutes after the subcutaneous administration of 0.4 mg. it diminished to

170/80 and remained near this level for the next hour. In a case of essential hypertension 0.3 mg. subcutaneously was followed by a fall from 166/88 to 120/70 in 10 minutes; the initial pressure was regained 20 minutes later. Another case of essential hypertension was given 0.9 mg. by mouth. The pressure, which ranged between 210/90 and 185/95 during the preliminary period, diminished very slowly until 3 hours after the administration of the drug, it reached 138/70. The face was markedly flushed at this time. The pressure rose thereafter but did not regain its initial level within 5 hours. Four other cases showed little or no diminution of pressure after the drug.

In contrast to these acute effects, attempts to cause prolonged reduction of pressure in hypertension by courses of the drug by mouth have been uniformly unsuccessful. Oral dosage ranging from 0.2 to 0.8 mg. t.i.d. continued for several days had no effect in 4 cases. Daily and twice daily subcutaneous injections of 0.4 mg., continued for 2 weeks, had no lasting effect on another case.

In no instance was the decrease in blood pressure following carbaminoylcholine rapid enough to make the patient uncomfortable, a marked contrast to the abrupt action of subcutaneous doses of acetyl- β -methylcholine.

Untoward Effects. Doses of doryl, easily tolerated by some, make others extremely uncomfortable. These untoward effects warrant detailed description.

Early in the study of the drug the author took increasing amounts by mouth. A dose of 0.6 mg. caused very little effect. Three days later he took 0.9 mg. with the following result. He sat for at least 10 minutes in a chair before each estimation of pulse rate and blood pressure, and walked about and interviewed patients in the interim.

- 9.20 A.M. Pulse 82; blood pressure 118/74. Feeling very well.
- 9.25 Took 0.9 mg. Doryl by mouth (three 0.3 mg. tablets followed by water).
- 9.45 Pulse 82; blood pressure 104/70. First sensation, attributable to drug, peristaltic waves and epigastric discomfort. Passed flatus.
- 10.10 Pulse 74; blood pressure 108/70. Peristaltic waves felt frequently. Sinus arrhythmia.
- 10.15 Bowels moved, soft formed stool (they had moved before at 7.30 A.M. that morning). Queer sensation noted in eyes, probably an effect on accommodation.
- 10.35 Face flushed and feels hot. No frank sweating.
- 11.00 Pulse 72; blood pressure 108/78. Flush of face and eye sensation continue. Trifling sweating of palms.
- 11.15 Slight salivation noted. Slight cramps now accompany peristaltic waves.
- 12.00 NOON Pulse 70; blood pressure 100/78. Slight lachrymation in addition to the above.
- 12.15 P.M. Weak and light headed when trying to walk. Belches.
- 12.30 Pulse 66; blood pressure 110/80. Electrocardiogram showed nothing abnormal.

- 12.40 Weakness forced him to lie down. Very flushed with strong sensation of heat in face and ears, slight headache, very slight salivation, practically no sweating, occasional consciousness of peristaltic wave.
- 1.30 Feeling a little better, ate light lunch. Headache better.
- 2.50 Pulse 100; blood pressure 110/65. Still feeling badly in an indefinable way. Weakness and shortness of breath on walking about. Glad to stay in chair.
- 3.15 Pulse 90; blood pressure 120/65. Flush continues. Some epigastric and precordial discomfort after walking about.
- 4.45 Pulse 72; blood pressure 115/28. Better, flush almost gone, other symptoms gone.
- 5.30 Walked 400 yards and found himself still somewhat weak. Took atropine sulphate 0.3 mg. subcutaneously. Recovered quite rapidly thereafter.

The symptoms described above, especially malaise and vague gastro-intestinal symptoms have occurred in patients. One man experienced them as soon as he began to take 0.4 mg. t.i.d., another after taking 0.4 mg. once daily for over a month. In contrast to this, single doses of 2 mg. have been taken by some subjects without discomfort. The irregularity of the untoward effects of the drug deserves emphasis.

After subcutaneous administration more uncomfortable effects sometimes appeared. A patient with rheumatic heart disease and auricular fibrillation, in good cardiac compensation, was given 0.6 mg. subcutaneously at noon. Very little change of blood pressure or pulse rate followed. However, 20 minutes after the injection she complained bitterly of abdominal pain and nausea. Atropine, 0.6 mg. subcutaneously, stopped the slight sweating, but pain persisted, and the dose of atropine was repeated 15 minutes later. Discomfort passed off slowly and the patient said she felt badly all the rest of the day.

A patient with diabetic peripheral vascular disease, who had previously suffered from diarrhea, was unable to take 0.2 mg. subcutaneously without prompt return of the diarrhea.

An asthmatic patient given 0.2 mg. subcutaneously had a typical asthmatic attack within 10 minutes. Atropine, 0.6 mg. subcutaneously, promptly relieved it.

The only reaction at all alarming occurred in a man with peripheral vascular disease who had lost one leg and was suffering greatly from pain in the other. He was given 0.6 mg. subcutaneously. The blood pressure and pulse rate, 130/86 and 100 before the drug, both fell slowly. Twelve minutes later they were 103/70 and 64. At this time flushing, sweating and abdominal pain were present. One half hour after the drug the patient began to look and to feel very badly. The systolic pressure was found to be 80, the pulse 56. Atropine, 0.6 mg. subcutaneously, was given at once, and the blood pressure rose to 140/100 within 3 minutes. The other choline effects disappeared within 30 minutes. The pain in his foot was not relieved.

Effect of Atropine on the Action of Carbaminoylcholine. In animal experiments atropine abolishes the parasympathetic effects of carbaminoylcholine but the nicotine-like action is not affected. Therefore atropine cannot be expected to antagonize the effect of carbaminoylcholine with the rapidity and completeness with which it abolishes the action of acetyl- β -methylcholine¹⁵ (mecholyl), a drug without noteworthy nicotine-like effect.¹² Experience supports this expectation.

The effect of atropine on the action of carbaminoylcholine has been tested in 12 normal subjects. Atropine 0.6 mg. subcutaneously, given about 20 minutes before carbaminoylcholine, completely blocked the detectable effects of 0.3 mg., greatly diminished the effects of 0.4; and had a slight but definitely antagonistic effect on the action of 0.8 mg. On the other hand atropine 0.3 mg. subcutaneously given 20 minutes before a dose of 1 mg. carbaminoylcholine subcutaneously did not notably antagonize the uncomfortable effects and more atropine had to be given.

After the effects of a large subcutaneous dose 0.8 to 1.0 mg., of carbaminoylcholine had manifested themselves, the subcutaneous injection of 0.3 mg. of atropine did not cause any noteworthy diminution of the severity of the symptoms. Under similar circumstances 0.6 mg. of atropine was followed by a slow but definite diminution of the uncomfortable effects which disappeared completely within 30 minutes.

The experience in the clinic has been similar. Subcutaneous doses of 0.6 mg. of atropine cause slow diminution of uncomfortable effects following carbaminoylcholine.

Therapeutics. The best use that we have found for carbaminoylcholine is in the relief of pain in certain cases of peripheral vascular disease. Two of these deserve report in detail.

Case Report. CASE 1.—A. E., aged 49, of German ancestry, had had intermittent claudication in both legs for over 20 years and phlebitis at intervals since that time. Six weeks before admission, rest pain began in both feet which turned purple in color but developed no lesions. The pain was described as "burning" and "like hundreds of needle pricks." It occurred in paroxysms. Three injections of typhoid bacilli were given in another hospital with transient relief only once after a severe reaction. Repeated intravenous injections of 2.5% sodium citrate did not help. Injection of his left posterior tibial nerve with procaine caused no rise of skin temperature in the area supplied.

On admission to this hospital the pain was chiefly in the left foot and so intense that the patient would scream. Morphine sulphate, 1 grain, afforded little, if any, relief. No pulsation could be felt in any vessels below the femorals. Both feet were cyanotic when dependent, blanched while elevated. The nails were atrophic and there were numerous petechiæ in the involved skin. The ankle jerks were absent. There were no lesions. Histamine reaction showed no wheal on either foot, the flare was doubtful. Warming the hands failed to increase the skin temperature of the feet. The diagnosis was thromboangiitis obliterans.

The patient's feet were placed in a thermoregulated cradle and daily treatments of suction and pressure were given to the left leg. It was

soon discovered that small subcutaneous doses of acetyl- β -methylcholine (mecholyl 2.5 mg.) relieved the pain promptly but only for a few minutes. Larger doses caused more side effects without producing more relief. Large doses of the same drug by mouth (2 gm. daily) had very little effect on the pain. Mecholyl 10 mg. subcutaneously, dissolved in ethyl lactate to slow absorption, produced relief only a little more prolonged than that secured by injection of the aqueous solution. The ethyl ether of β -methylcholine, 20 mg. by mouth every 3 hours, also caused only slight relief.

Carbaminoylcholine was then tried; 0.3 mg. by mouth had little if any effect but 0.25 mg. subcutaneously was followed promptly by complete relief which lasted several hours. Accordingly this dosage was administered every 4 hours. Practically complete relief followed. After this he needed no other sedative. Several days later atropine was administered for another purpose and pain returned at once.

The patient received 0.25 mg. carbaminoylcholine every 4 hours from April 22 to May 9 with almost complete freedom from pain. On the latter date, salt solution was substituted for the drug without the patient's knowledge. Pain promptly returned, although it was not so severe as before, and carbaminoylcholine administration had to be resumed. On June 3, a second unsuccessful attempt was made to withdraw the drug, mild pain recurring. On June 12, the drug was withdrawn successfully and he was discharged free of pain, his feet, though still far from normal, a much better color than on admission.

There were no disagreeable side effects from the drug at any time.

CASE 2.—D. F., aged 30, with thromboangitis obliterans, was a powerfully built young man of English extraction, an excessive consumer of tobacco. In 1933, he began to have trouble with cold and painful fingers. Infections developed which lasted all summer. In the fall the fingers healed but similar trouble developed in the toes. Several toes became infected causing severe pain and requiring 6 months for healing. In the meanwhile the fingers again became involved so that he had been in almost constant pain for 3 years prior to his admission. Finally the application of carbolated vaseline was followed by gangrene.

On admission in December, 1935, the dorsalis pedis, the posterial tibial and the left radial pulses could not be felt. The right great toe was ulcerated to the bone, the tip gangrenous. The tip of the left great toe was gangrenous. Both feet showed rubor on dependency and pallor on elevation, the color changes being largely in the toes. The fingers were also cyanotic when dependent, the skin being thickened and the nails atrophic. There were small ulcers at the tip of the left thumb and left fifth finger. Roentgen ray showed definite bone destruction of the distal phalanx of the left great and second toes. Spinal anesthesia was not accompanied by increased skin temperature of either foot.

The patient was given a thermoregulated foot cradle which he used constantly. The lesions had routine surgical care. He was induced to stop smoking. Carbaminoylcholine, 0.4 mg. subcutaneously, was administered repeatedly and was regularly followed by complete relief of pain, beginning about 20 minutes after the injection and lasting 4 hours or longer. He was placed on this dosage p. r. n. every 5 hours for pain, and at first required two injections a day to keep him comfortable. Slight salivation, slight sweating, and increased consciousness of heart action, were usually noted by the subject after each injection but they did not annoy him. Hypodermic injections of saline solution, substituted without the patient's knowledge caused no relief and were identified within a few minutes as not being the right medicine.

On two occasions pain developed which was not relieved by carbaminoylcholine. In both instances retained pus was discovered under a crust. When this had been drained the drug again relieved the remaining pain.

The gangrenous areas slowly detached themselves. The exposed terminal phalanx of the left great toe was removed surgically. The lesions healed steadily. After 1 month he was nearly free from pain without the drug and, not requiring hypodermics, he was placed on doryl 0.4 mg. by mouth twice a day. He was discharged on this dosage, but after taking it for about 2 months he began to experience nausea after each dose. Therefore the dose was reduced to 0.2 mg. twice daily, which could be taken without discomfort. When seen on April 1, the lesions had healed except for a tiny spot on the right great toe, and he was told to discontinue doryl as soon as the weather became warm. When examined in October, 1936, all lesions had been healed for many months, the pulse had returned to the left radial and all signs of his disease showed marked improvement. He had been working as a truck driver all summer.

Carbaminoylcholine has been used at some time during the course of 20 cases of peripheral vascular disease. In about one-fourth of these definite relief of rest pain was secured by the drug at some time during their stay in the hospital. This experience has led me to expect that relief of pain will not be secured when gangrene is ascending the limb or in the presence of infection not adequately drained. In other conditions some degree of relief often follows the drug, especially if the pain is markedly paroxysmal in character. In a few cases the relief secured by the drug was far greater than which had followed morphine.

Little can be said about the effect of the drug on the healing of lesions in peripheral vascular disease because other methods of treatment were used in every instance.

In my hands carbaminoylcholine has had no important action on the heart. A case in an attack of paroxysmal auricular tachycardia was given 0.4 mg. without altering the rhythm. Later in this attack, and on 3 other occasions, 30 mg. of acetyl- β -methylcholine caused immediate termination of the tachycardia.¹⁴

Two patients with frequent ventricular extrasystoles were given 0.4 and 0.6 mg. subcutaneously without any effect on the frequency of their arrhythmia.

Our one attempt to aid a case of postoperative urinary retention by means of the drug was not successful. The patient still had to be catheterized after repeated doses of 0.6 mg. subcutaneously.

Discussion. It is of interest to compare the clinical action of the two active choline derivatives, carbaminoylcholine (doryl) and acetyl- β -methylcholine (mecholy), to emphasize their differences, and to indicate the type of situation in which each is superior to the other.

After subcutaneous injection the action of doryl comes on slowly and gradually in sharp contrast to the vigorous effects which so quickly follow an injection of mecholy. The duration of action of the former drug far outlasts that of the latter.

Mecholy has more action on the heart and blood-vessels, in proportion to its other effects, than has doryl. The largest doses of doryl that can be tolerated cause severe gastro-intestinal symptoms before there is much effect on blood pressure, in most instances.

In contrast to this, large doses of mecholyl cause a sharp drop in blood pressure with profound vagus-like effects on the heart without uncomfortable gastro-intestinal effects. Doryl has had no effect on the cardiac arrhythmias in the cases I have studied. Obviously therefore we must expect mecholyl to be superior to doryl in the production of cardiac and vascular effects of short duration.

Doryl should be superior where prolonged effects, other than cardiac, are desired. For instance, the gastro-intestinal effects following a subcutaneous injection of mecholyl cannot be secured without making the patient uncomfortable from the diminished blood pressure; doryl should be far superior to mecholyl for such a purpose. However, a new choline derivative, carbamino- β -methylcholine,^{13b} introduced by Simonart in 1935, has appeared, in our preliminary trials, to be superior to doryl in the production of gastro-intestinal effects. For this reason investigation of the gastro-intestinal action of doryl has not been pushed.

After oral administration doryl is irregular and cumulative in its effects. Uncomfortable symptoms, chiefly malaise and nausea, appear in some persons after dosage less than one-half of that easily tolerated by others. Mecholyl in large doses by mouth practically never produces any untoward effect other than slight gastric irritation.

Like mecholyl and certain other choline derivatives doryl will cause asthmatic attacks in those subject to this disease. These induced attacks can be promptly relieved by atropine. An excessive fall of blood pressure, seen in 1 case, was also promptly restored by atropine. But atropine has a slower and less pronounced effect on the abdominal discomfort, nausea, and malaise, that follow large subcutaneous doses of doryl. Perhaps some of this discomfort is due to the nicotine-like effects of doryl, which are not antagonized by atropine in animal experiments.

Both doryl and mecholyl relieve pain in certain cases of peripheral vascular disease. If hypodermic medication is desirable in such a case, doryl is far superior. For oral administration the choice is harder to make. Doryl is far less expensive. But in some cases I have obtained most satisfactory results with tablets of mecholyl bromide. When the patients cannot be under the observation of a physician, they are on safer ground if they take mecholyl, a drug without cumulative effects and well tolerated in very large dosage when taken by mouth.

It is of interest that striking relief of pain can be secured by doryl in certain cases of peripheral vascular disease without any increase in skin temperature of the affected part. This raises the question whether the relief secured is due to something else than vasodilatation. In my opinion, the skin temperature method of estimating peripheral blood flow is too crude to permit one to place much emphasis on a negative result. So I attribute the relief of pain

to vasodilatation of a grade too slight, or in vessels too deep, to be detected by this method.

Conclusions. Carbaminoylcholine chloride is one of the most powerful drugs known. Studies have been conducted on its action after subcutaneous and oral administration to 26 normal volunteers and to a larger number of patients. Special studies of its effect on the heart and circulation have been made in a small group of cases.

The information now at hand concerning its dosage, action, and untoward effects, is sufficient to warrant its cautious use in those cases that its action seems adapted to benefit. The drug causes striking relief of rest pain in certain cases of peripheral vascular disease.

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THE USE OF ACETYL- β -METHYLCHOLINE CHLORIDE BY IONTOPHORESIS IN PERIPHERAL VASCULAR DISEASES.

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CONSIDERABLE attention has been given during the past 5 years to disturbances of the circulation in the extremities. Excellent strides have been made along the lines of investigation of circulating efficiency. The added interest in this comparatively new field has resulted in stimulating the desire for correcting these conditions. Newer methods of treatment including drugs and physiotherapy have been advocated.

Among the drugs, the choline group attracted the attention of many investigators, including Simonart,¹² Hunt and Taveau,⁵ Dale,² and others. Acetylcholine was found to possess vasodilator properties which indicated that it would be valuable in the treatment of vascular diseases. However, its action was marred because of a nicotine-like effect upon the vasomotors. Further experimentation

and investigation by Major and Cline¹⁰ resulted in the production of acetyl- β -methylcholine chloride, known as mecholyl.

Pharmacologically, mecholyl is physiologically antagonistic to epinephrine. It was presumed that it would be beneficial in those cases where there were evidences of diminished parasympathetic or excessive sympathetic tone.

The possibilities of clinical application of acetyl- β -methylcholine chloride were studied by Kovács, Wright, Starr *et al.*,¹⁴ Goldsmith^{4a, b} and others. It has been employed in the treatment of various conditions other than vascular diseases, such as arthritis,¹ paroxysmal tachycardia,¹³ neurogenic bladder,³ pelvic inflammatory disease⁶ and chronic leg ulcers.⁹

Methods of Administration. Mecholyl may be given in one of three ways: First, subcutaneously, in doses of 20 to 25 mg., producing prompt effects. Second, it may be given orally in larger doses. Goldsmith employed 1000 to 1500 mg. The effects of the drug appear within 15 to 75 minutes. Smaller doses (100 mg.) were also found to be effective in some cases of Raynaud's disease. The third method of administration is by ionization.

Technique of Mecholyl Iontophoresis. (1) Aqueous solution of 0.25 or 0.2% is employed. (2) Asbestos paper or cotton bandage, which we prefer, is soaked in the mecholyl solution and wrapped about the part to be treated. (3) A spiral block-tin electrode is applied and attached to the positive pole of the galvanic machine. Mecholyl, being an alkaloid, takes a positive charge. (4) A broad dispersive pad is placed firmly against the back. This is attached to the negative pole. (5) Current is turned on slowly, gradually increasing up to 15 to 20 ma. This may later be increased to 25 or 30 ma. Allowance should be made for a slow rise during treatment. (6) Treatments should last from 20 to 30 minutes. (7) Gradually reduce until off. It should not be turned off abruptly. (8) The part should then be thoroughly dried. Patients susceptible to asthma should be treated cautiously because an asthmatic attack may be precipitated. Atropine will invariably control and check any untoward effects which may arise.

Effects of Treatment. During treatment there may be a sensation of fullness and warmth in the extremity. Salivation may occur. Flushing and erythema of treated part or a goose-flesh appearance may be evident after the wrappings have been removed. Sometimes a lowering of blood pressure may occur. We have not experienced any untoward effects on any of our patients who have been treated by iontophoresis. On 2 patients we attempted to supplement ionization by giving 15 to 25 mg. of mecholyl subcutaneously. There was prompt flushing of the face, profuse sweating, epigastric distress and nausea developed. These symptoms were controlled instantly by giving atropine.

The prompt relief we have noted concurs with the experiences of other observers. The results of the treatment by iontophoresis may not be apparent immediately. As a rule, the patients do not experience much until $\frac{1}{2}$ hour or more has elapsed, and then there is a sensation of warmth in the extremities. Fatigue is lessened.

The comfort that results from the treatment may last for several hours and in some cases for a day or two. Occasionally, some complain of an itching sensation over the parts that have been treated, and a rash. This was noted in 3 patients. The rash is punctate in character and looks like rose spots.

In this paper we shall limit ourselves to the use of mecholyl* by iontophoresis for the treatment of peripheral vascular diseases.

Thirty patients were treated and about 350 treatments were given. These patients were not selected. They were ambulatory. There were 11 cases of thromboangiitis obliterans, 8 were diabetic, 8 had vasospastic arterial disease, and 3 were cases of phlebitis.

The results of the treatments have been arranged in tabular form and will be discussed under the headings of disease groups.

Thromboangiitis Obliterans (Buerger's Disease). This group is looked upon as the test for any form of treatment offered in the therapy for vascular diseases. Eleven patients of various ages and various degrees of the disease were embraced in this group. Some were early cases, others had symptoms dating back for years.

TABLE 1.—RESULTS OF TREATMENT OF 11 CASES OF THROMBOANGIITIS OBLITERANS (BUERGER'S DISEASE).

Case.	Name.	Age.	Sex.	Duration, yrs.	No treatments.	Improvement of symptoms.						General improvement.				Other treatments.	Remarks.
						Cramps.		Fatigue.		Pains.		Good.	Some.	Temporary.	None.		
						Yes.	No.	Yes.	No.	Yes.	No.						
1	B. B.	21	M	3	19	x	..	x	..	x	..	x	Vaccine	1/2 block/5 to 6.*	
2	R. C.	29	M	3	11	x	..	x	..	x	..	x	Ganglionectomy	1/2 block/2 to 3.*	
3	H. D.	59	M	7	7	x	..	x	..	x	..	x	Na citrate	1/2 block/3 to 4.*	
4	J. K.	65	M	17	54	x	..	x	..	x	..	x	Ulcer—toe healed.	
5	M. L.	62	M	1	10	x	..	x	..	x	..	x	..	x	...	Coronary art. disease.	
6	L. L.	61	M	4-5	22	x	..	x	..	x	..	x	1/2 block/10 to 12.*	
7	H. M.	49	M	1	3	x	..	x	..	x	..	x	..	x	...	Coronary art. disease.	
8	A. B.	57	M	3	3	x	..	x	..	x	..	x	Na citrate	Coronary art. disease.	
9	H. C.	69	M	2	6	x	..	x	..	x	..	x	..	x	NaCl 2%	Coronary art. disease.	
10	S. L.	62	M	1	6	x	..	x	..	x	..	x	..	x	
11	P. S.	60	M	2	7	x	x	
						8	2	8	2	5	4	3	3	2	3		

* Indicating walking distance before and after treatments.

The best results were obtained in Cases 1, 4 and 6.

Case Notes. CASE 4.—J. K., gave a history of vascular disturbances with questionable diabetes. Twelve years ago, gangrene occurred, resulting in amputations of the left leg and 2 toes of the right foot. There was a chronic trophic ulcer of 2 years' duration, at the site of amputation of the distal phalanx of the middle toe. After a series of treatments, the patient noticed a marked improvement with complete healing of the ulcer.

CASE 6.—L. L., also showed very gratifying results. He received a series of 22 treatments, making rapid progress in a few weeks (reporting twice

* Mecholyl was kindly supplied by Merck and Company, Inc.

weekly). Originally he could not walk more than $\frac{1}{2}$ block without discomfort. Toward the later period of our observations he could walk 10 to 12 blocks.

CASE 1.—B. B., responded well to treatment with a subsidence of all symptoms. Three others showed some improvement. Two were benefited temporarily while they were receiving treatments.

There were 3 failures. One was treated 3 times and was unable to continue because of a cardiac condition which subsequently was the cause of his death. The second, Case 5 (M. L.), after 10 treatments said there was some diminution of the pain, but on the whole was not benefited. The third, Case 11 (P. S.), had arteriosclerosis obliterans with a suggestive clinical picture of Buerger's disease.

Comment. The definite improvement of 3 cases (27%) and some improvement in 3 others, a total of 54% who were benefited, indicates that mecholyl does help. If we add the 2 patients who manifested temporary improvement, the total would be increased to 8 (72%). The fact that there is warmth and flushing of the skin and the rise in skin surface temperature, which has been definitely demonstrated by others, suggests that the drug has penetrated the tissues and vasodilatation has resulted. Kovács and Wright were not encouraged by their results in the occlusive forms of vascular disease. On the other hand, Goldsmith and others have noticed definite reactions in this group.

No form of treatment thus far has been able to benefit all cases of Buerger's disease. There is too much structural change to overcome. The object of the treatment is to attempt to establish the best possible collateral circulation so that nutrition to the tissues may be carried on and the symptoms relieved. The success of any treatment will probably depend upon the extent of the lesions in the vessels and will also depend upon how early treatment has been instituted.

TABLE 2.—EFFECTS OF MECOLYL UPON 8 CASES OF DIABETES WITH VASCULAR DISTURBANCES.

Case.	Name.	Age.	Sex.	Duration, yrs.	No treatments.	Improvement of symptoms.						General improvement.				Other treatments.	Remarks.
						Cramps.		Fatigue.		Pains.		Good.	Some.	Temporary.			
						Yes.	No.	Yes.	No.	Yes.	No.			None.			
1	J. B.	62	M	25	25	x	..	x	x	Suspected Buerger's.	
2	I. S.	46	M	13	13	x	..	x	x	3 to 4 blocks/many.	
3	C. S.	50	F	5	8	x	..	x	x	Potential gangrene.	
4	S. W.	49	F	5	3	x	Local gangrene—lost.	
5	M. O.	48	F	6	6	x	x	..	x		
6	J. K.	59	F	5	6	x	..	x	Presumably neuritis.	
7	M. C.	67	M	14	x	x	..	x	x	2 blocks/4 to 5.	
8	J. G.	69	M	3	4	x	..	x	Na citrate	..	Suspected Buerger's.	
						4	..	7	..	1	4	5	1	..	2		

Diabetic Arteritis. In the diabetic group, 5 of the 8 patients were improved (62.5%); 1 said she felt better and 2 were not benefited

(25%). Of the failures, both said the pain was not relieved. Case 5 (M. O.) said there was some temporary improvement but was listed as a failure. Case 6 (J. K.) was a mild diabetic who did not require insulin. She complained of severe pains in the legs. Although the circulatory tests showed some impairment of circulation, it was presumed that the pains were more likely due to some neuritic condition. After a series of 6 treatments she said the pains were the same and that no improvement could be noted.

The 5 patients who responded to the treatments were definitely better. They were insulin cases and showed the usual clinical signs and evidences of occlusive vascular disease. Cases 1 and 7 could practically be included in the Buerger disease group, and Case 3 (C. S.) on 2 occasions had threatened gangrene, but fortunately managed to escape serious complications. The improvement in this series was evidenced by the fact that the patients developed greater endurance for work and a subsidence of symptoms in most of them. Case 1, although he was unable to walk a greater distance, said he was able to manage his business affairs which necessitated considerable effort by being on his feet most of the time. Others such as Cases 2 and 7 said there was a noticeable change and both could navigate longer distances without discomfort. Case 8 (J. G.), a diabetic with occlusive vascular disease, complained of discomfort and pain in the left leg and foot. There was a good response to mecholyl. After the third treatment the patient was able to get about without discomfort.

The above studies would indicate that mecholyl will benefit the diabetic with vascular disturbances in 75 to 80% of the cases. It should be of particular value to the patients who are early recognized as cases of potential gangrene, *i. e.*, where evidences of impaired circulation are detectable. Given an early start with proper care, efforts to build up a collateral circulation should help materially in warding off gangrene.

Vasospastic Disturbances. Eight patients belonged to this group of vascular disorders. The first case (M. B.) showed evidences of Raynaud's syndrome and a suggestive phlebitis of the deep veins in the legs. Case 2 (S. T.) also had a clinical picture of Raynaud's with an orthopedic condition of the feet. The third case (B. K.) showed evidences of impaired circulation in the legs, vasospastic type, but did not conform to the classic picture of Raynaud's. They felt improved while taking treatments. The latter 2 patients felt well for sometimes after the treatments were discontinued but subsequently there was a recurrence of symptoms.

Case 4 (H. E.) showed the classic picture of Raynaud's disease with beginning trophic disturbances in the tip of the index finger. It was blanched nearly all the time and appeared to be ready to break down. After a series of 10 treatments, the tissues at the tip seemed healthier and pink. There was a more general improvement as well.

TABLE 3.—EFFECT OF MECHOLYL UPON 8 CASES OF VASOSPASTIC DISTURBANCES.

Case.	Name.	Age.	Sex.	Duration, yrs.	No treatments.	Improvement of symptoms.						General improvement.				Other treatments.	Remarks.
						Cramps.		Fatigue.		Pains.		Good.	Some.	Temporary.	None.		
						Yes.	No.	Yes.	No.	Yes.	No.						
1	M. B.	19	F	2	39	x	..	x	..	x	x	Raynaud's. Raynaud's orthopedic condition. Symptoms recurred. Raynaud's and scleroderma. Raynaud's.	
2	S. T.	25	F	1½	10	x	..	x	x		
3	B. K.	34	F	3	15	x	..	x	..	x		
4	H. E.	45	F	1	9	x	..	x		
5	S. N.	46	M	1	8	x	..	x	..	x	Mecholyl inj.	Mecholyl inj.	
6	D. V.	40	M	1	5	x	..	x	..	x	..	x		
7	S. V.	40	F	6*	5	x	..	x	..	x	Phlebitis.	
8	S. B.	39	F	4	6	x	..	x	..	x	Phlebitis.	
					3	..	7	..	8	..	5	1	1				

* Months.

Case 5 (H. N.) was another patient with Raynaud's disease associated with a fairly advanced scleroderma. The fingers were stiff and exhibited the typical tautness of the skin. He also responded nicely to iontophoresis-mecholyl. After 8 treatments the skin was not so tight and he could use his fingers. He was quite enthused when he discovered that he would work all day without feeling exhausted.

Cases 6, 7 and 8 were of a milder form. Two of them had a suggestive phlebitis of the deep veins with evidences of impaired circulation based upon studies of circulatory function tests. All responded to treatment.

Comment. Because of its vasodilator properties it is quite understandable that acetyl- β -methylecholine chloride exerts a favorable influence upon vasospastic diseases. The beneficial effect upon this group of vascular disturbances has been consistently noted in reports from those who have investigated this drug both experimentally and clinically. Some had a return of symptoms afterward. However, the improvement lasted for some considerable time after the treatments were discontinued. This was not unexpected. After all, it is unreasonable to expect this drug to be judged merely by its ability to cure.

Phlebitis. Mecholyl was used in this group as an experiment. Kovács and Wright were elated with the results in the treatment of chronic ulcers presumably due to varicose veins. These ulcers were of a stubborn nature and resisted all other treatment. With mecholyl by iontophoresis they were able to cure every case. In their preliminary report they mention 9 cases and in a later paper have added a much larger number of patients with excellent results. Because of their experience, we applied this form of therapy to

3 patients with phlebitis—acute and subacute (Table 4). Two other patients in the vasospastic group were suspected of having phlebitis but were not included in this series.

TABLE 4.—EFFECTS OF MECHOLYL UPON 3 PATIENTS WITH PHLEBITIS.

Case.	Name.	Age.	Sex.	Duration, yrs.	No. treatments.	Improvement of symptoms.						General improvement.				Other treatments.	Remarks.
						Cramps.		Fatigue.		Pains.		Good.	Some.	Temporary.	None.		
						Yes.	No.	Yes.	No.	Yes.	No.						
1	I. W.	35	M	1	9	..	.	x		x	..	x		..	Vaccine	Acute.	
2	N. E.	54	M	1	3	.	..	x	.	x	..	x	Subacute.	
3	T. G.	40	F	1	8	x		x		x	.	x	Deep veins and mild cramps.	
						1		3		3		3					

Comment. Although this is a small series, yet we feel that some comment is pertinent here. There was a striking response in the relief of fatigue. Later the pains subsided. We cannot say why or how mecholyl helps this group. We know that in Buerger's disease a definite relationship seems to exist between the diseased veins and arteries and that the phlebitis may be a primary factor in the development of thromboangiitis obliterans. It is possible that in the above-mentioned patients the phlebitis produced a more or less degree of vasospasm of the nearby arteries and that mecholyl was instrumental in overcoming this spasm.

Effects of Mecholyl Upon Symptoms. The results upon the various disease groups and the symptoms have been arranged for comparison in Table 5. The total benefited by treatment was 22 (73%). Of this group, the highest percentages were among the vasospastic and phlebitis patients. The lowest percentages was in the Buerger disease series (55% of these patients responded to treatment). The diabetic group was more encouraging, 75% of the patients were benefited by iontophoresis.

From the above table we note that mecholyl has an excellent influence upon such symptoms as fatigue and cramps and only a moderate effect upon pain. Sixteen of the 18 patients who had cramps felt better and 25 of the 27 patients who complained of fatigue were considerably relieved. This response was noticeable in all the groups.

Pain did not seem to be influenced by mecholyl to the same extent as the other symptoms. Out of 25 patients who complained of pain, 17 were relieved (66%) and 8 did not respond. The entire number of failures were among the Buerger disease cases and diabetes. It is to be remembered that pain may result from arterial spasm,

TABLE 5.—ANALYSIS OF THE EFFECTS OF MECHOLYL UPON SYMPTOMS IN THE 4 DISEASE GROUPS.

Disease group.	Symptoms improved.						Results.				Total.			
	Cramps.		Fatigue.		Pains.		Good.	Some.	Temporary.	None.	Benefited.		Failures.	
	Yes.	No.	Yes.	No.	Yes.	No.					Total.*	%	Total.†	%
Buerger's. . .	8	2	8	2	5	4	3	3	2	3	6	55	5	45
Diabetic. . .	4	..	7	..	1	4	5	1	..	2	6	75	2	25
Vasospastic. . .	3	..	7	..	8	..	6	1	1	..	7	87	1	13
Phlebitis. . .	1	..	3	..	3	..	3	3	100		
							17	5	3	5				
Totals. . .	16	2	25	2	17	8	22		8					
Per cent. . .	89	..	92	..	66	..	73		27					

* Total benefited—include those with some improvement.

† Temporarily improved—included with the failures.

anoxemia and from nerve influences, either inflammatory or because of deficient blood supply to the nerves. Mecholyl may contribute to the relief of pain probably when it is brought about by spasm or anoxemia. This drug presumably cannot cope with the situation when the pain is caused by other influences.

The total percentages of those benefited compares favorably with other forms of treatment. The practicability of iontophoresis is further emphasized because it can be employed in all cases of vascular diseases where the circulation is impaired.

Conclusions. Acetyl- β -methylcholine chloride (mecholyl) is recognized by investigators as the most desirable preparation of the choline group for peripheral vascular disease.

Iontophoresis, or ionization, is the more direct and logical method of administering it in vascular disturbances. It is simple and practical.

In a series of 30 patients observed in the course of over 350 treatments there were no serious untoward effects. Twenty-two patients (73%) were benefited, 3 were helped only temporarily and were added to the 5 failures, giving a total of 8 (27%).

The best results were obtained in the vasospastic group, 87% responding favorably and excellently in the small phlebitis series; the diabetic cases showed a 65% favorable response and the Buerger disease group 55%.

Symptomatically, mecholyl had a decided influence upon fatigue and cramps regardless of the underlying lesions. It did not control the pain so readily, particularly in the diabetic and thromboangiitis groups.

The results of our observations evidently concur with the findings of those who investigated the pharmacologic and physiologic proper-

ties of acetyl- β -methylcholine chloride and suggested that it had possibilities in the treatment of peripheral vascular diseases. While it does not cure, mecholyl undoubtedly does give relief in many cases by improving and increasing peripheral circulatory function.

We wish to express our grateful acknowledgement to the Medical, Surgical and Orthopedic Departments for their coöperation and the privilege of observing their patients, and to Dr. Ross V. Patterson for his helpful suggestions.

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URINARY EXCRETION OF ARSENIC.

I. NORMAL SUBJECTS.

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THE literature is full of statements about urinary arsenic excretion, but there is a dearth of actual figures which can stand scrutiny. We undertook, therefore, to determine the daily excretion of arsenic in the urine of essentially normal individuals. The establishment of a "normal" value is not merely of academic interest; it is essential for diagnosis and for ascertaining the effects of therapy. Results obtained in disease or under specific medication can be interpreted only in the light of adequate, controlled experiments. Failure to produce such data discredits much that has been reported on the excretion of arsenic.

Fordyce, Rosen and Myers² tabulated analyses of "normal" urine varying from 0 to 18.5 mg. of arsenic in 100 gm. of *dried* specimen without committing themselves to an accepted normal. Presumably the specimens were casual samples obtained from clinic patients of uncertain dietary and medicinal habits. Such casual specimens are shown by us to be meaningless. Unfortunately the

investigation of Fordyce *et al.* cannot be evaluated readily since the results are expressed in terms of 100 gm. of moist or dry urine rather than on the basis of a volume or 24-hour excretion. There seems to be no valid reason for supposing that the elimination of arsenic parallels that of the total solids. Myers and Cornwall⁵ report for normal urine 0.4 mg. As per 100 gm. of dried specimen (Marsh method). In their opinion, normal urine rarely exceeds 0.1 mg. As per liter. According to a citation from Hills, of 260 samples from 180 patients 135 showed urinary arsenic, 5 varying from 0.3 to 0.5 mg. per liter.

Mayer⁴ cites Schwartz as examining 74 normals of whom 18.9% presented no arsenic, 55.5% showed 0.01 to 0.09 mg. per liter, 14% revealed 0.1 to 0.19 mg. per liter, and 11% varied from 0.2 to 0.69 mg. per liter of urine.

Griffon, Buisson and Bardou³ investigated the urinary output of arsenic in 33 persons (French) exposed only to "normal" amounts of the element. Their results varied from negative (3 instances) to 0.15 mg. As per 24 hours on "lacto-vegetarian" and "regular hospital" diets not otherwise described. Only 5 cases exceeded 0.05 mg. The series averaged 0.03 mg. per 24 hours (Griffon-Buisson method, 1933). These findings are significantly lower than those obtained in this country with different diets and chemical procedures.

The changing dietary habits of the American people and the ever-increasing use of arsenical insecticides (17,500,000 lbs. in 1919, 45,000,000 lbs. in 1923 and 58,000,000 lbs. in 1929, according to Myers *et al.*⁶) renders analyses performed abroad or in this country only a few years ago comparatively useless as indices of present-day conditions. Attempts to limit this dietary arsenic led one of us (D. W.) to devise a special diet.

Methods and Material. The Osterberg⁷ electrolytic Gutzeit procedure was used to ascertain the arsenic eliminated by the kidneys in 24 hours. Since it was not practical under routine conditions to take the entire specimen for analysis, a 25-cc. sample was arbitrarily selected for oxidation. (This amount required 15 to 20 cc. of H_2SO_4 .) The electrolytic step was carried out on an aliquot equivalent to 10 cc. of urine. Sensitized papers prepared by Osterberg's method were not satisfactory. It was found better to soak the papers in the bromide solution until needed. Before use, a strip was blotted dry between filter paper and a fresh cut made at the end to be exposed to arsine. The paper was checked frequently with standard solutions of arsenic.

With good test paper it was found possible to detect 0.0005 mg. of arsenic (as As), but precision was difficult below 0.0007 mg. A negative result merely indicated a concentration of less than 0.0005 mg. of arsenic in the sample subjected to electrolysis. Where, for

example, a 10-cc. sample was negative, it was reported as less than 0.08 mg. in a 24-hour volume of 1600 cc.

The subjects were members of the staff or persons hospitalized for presumably non-interfering conditions (*e. g.*, rheumatic fever, upper respiratory infections, epilepsy, hemophilia). The occupations, habits and histories of these individuals presented no unusual exposure to arsenic. No restrictions were enforced while on the "regular" institutional diet except the avoidance of those medications and cosmetics believed to be contaminated with arsenic. After a protracted period of trial-and-error, the arsenic-low diet was limited to dairy products, meats (except liver), fowl, eggs,

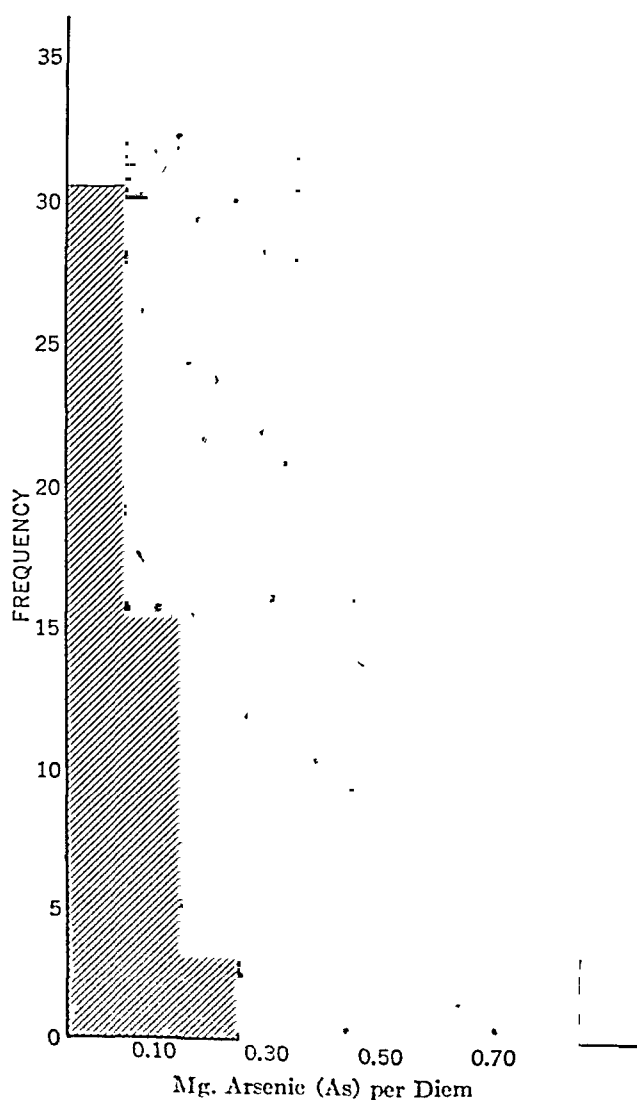


FIG. 1.—Frequency distribution of urinary arsenic range: Regular diet, 0 to 0.85 mg.; mean, 0.26 (163 cases); arsenic-low diet, 0 to 0.2 mg.; mean, 0.07 (46 cases).

potatoes, peas, turnips, squash, beets, carrots, breakfast cereals, rice, bananas, coffee, tea, sugar (small amount only), salt and pepper. (It is not claimed that these foods are arsenic-free; from our food analyses we know that they are not; their ingestion, however, leads to a minimal excretion of arsenic.) Breadstuffs, foil-wrapped and canned foods, soft or alcoholic beverages, fruit juices, vegetables and fruits known to be sprayed, tobacco, candy and commercial ice cream were forbidden.

Results. The frequency distribution of urinary arsenic is presented in Fig. 1. On the regular diet there are included 163 analyses with a variation from negative (18%) to 0.85 (mean 0.26) mg. of

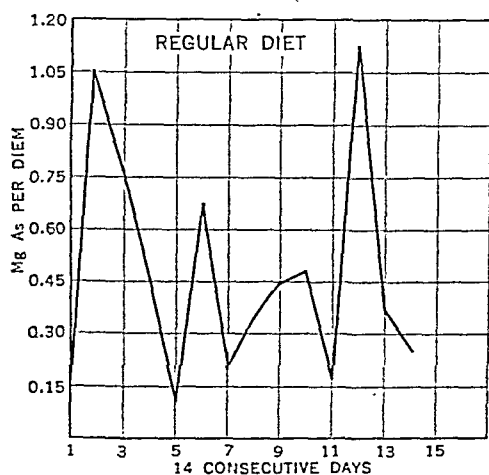


FIG. 2.—Urinary arsenic excretion.

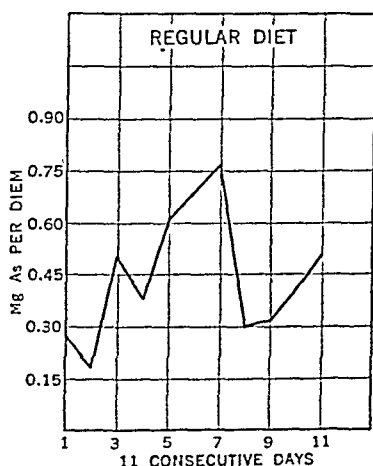


FIG. 3.—Urinary arsenic excretion.

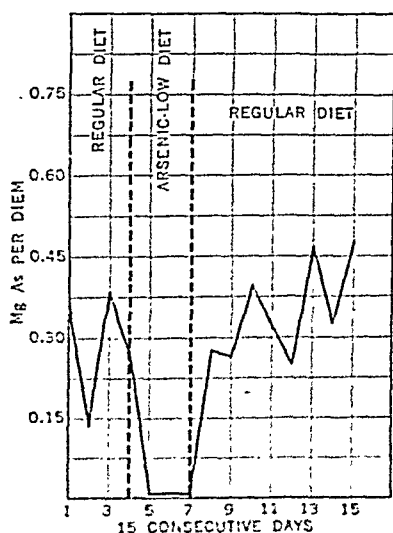


FIG. 4.—Urinary arsenic excretion.

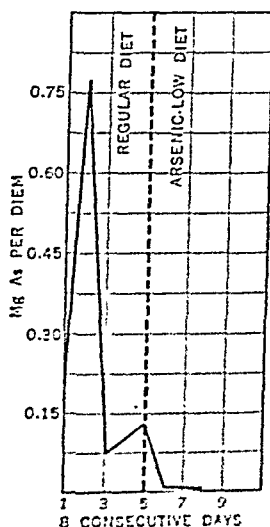


FIG. 5.—Urinary arsenic excretion.

arsenic *per diem*. Superimposed is a diagonally-hatched field depicting 48 analyses while on the arsenic-low diet, in which the range is from negative (62%) to 0.2 (mean 0.07) mg. of arsenic per 24 hours. Although over 400 24-hour samples were examined, data on scarcely more than half are presented. The remainder were not included because: 1, There was subsequent question of exposure to arsenic although the values in every instance lay within the range shown; 2, the results exceeded at least 4 times the ascertained mean (5 cases: 1.01, 1.07, 1.13, 1.13 and 2.4 mg. of arsenic); and 3, the test diets were unsatisfactory for several months (such results could not be tabulated either as "regular" or "arsenic-low").

The excretion of arsenic on various diets is shown in Figs. 2 to 5. The patient presented in Fig. 5 was followed for over 3 weeks, 15 days of which was on a minimum arsenic intake. Throughout the test period he maintained the low level of excretion. The greatest rate of elimination was 0.15 mg. of arsenic *per diem* and this could be ascribed to departure from the diet. Only by close attention to dietary detail is it possible to keep the urinary arsenic below 0.1 mg. per 24 hours.

TABLE 1.—URINARY ARSENIC EXCRETION IN INTERVALS COVERING FOUR DAYS.

Date, 1935.	Interval.	Volume, cc.	Arsenic (As).	
			Mg./100 cc.	Mg./specimen voided.
4/27 . .	7 A.M.—11 A.M.	60	0 023	0 014
	11 A.M.— 3 P.M.	900	0 011	0 099
	3 P.M.— 7 P.M.	490	Negative	Less than 0.02
	7 P.M.— 7 A.M.	1000	0 015	0 150
	24 hours	2450		0.26 + mg. <i>per diem</i>
4/28 . .	7 A.M.—11 A.M.	510	0 007	0 04
	11 A.M.— 3 P.M.	800	0 007	0 06
	3 P.M.— 7 P.M.	760	Trace	Less than 0.03
	7 P.M.— 7 A.M.	1320	Negative	Less than 0.04
	24 hours	3390		0 10 + mg. <i>per diem</i>
4/29 . .	7 A.M.—11 A.M.	370	0 015	0 06
	11 A.M.— 3 P.M.	370	0 007	0 03
	3 P.M.— 7 P.M.	605	0 007	0 04
	7 P.M.— 7 A.M.	1360	0 007	0 10
	24 hours	2705		0.23 mg. <i>per diem</i>
4/30 . .	7 A.M.—11 A.M.	700	0 019	0 13
	11 A.M.— 3 P.M.	440	Negative	Less than 0.01
	3 P.M.— 7 P.M.	1120	0 015	0 16
	7 P.M.— 7 A.M.	1040	0 007	0 07
	24 hours	3300		0 36 + mg. <i>per diem</i>

The urinary arsenic excretion by a normal individual on an unrestricted but known diet over a 4-day period is presented in Table 1, the collection of urine covering the four stated intervals

each day. It is apparent that the elimination of the metal is not constant nor confined to any time interval. Satisfactory studies on the urinary arsenic output cannot be made on samples taken at random.

Table 2 demonstrates the results of placing 2 individuals on the same diet, but without limiting them as to the amount of food or fluid consumed. Their response is by no means identical. Few or no data are available on individual variation in the urinary output of incidentally ingested arsenic. Presumably the healthy person rapidly eliminates such arsenic.

TABLE 2.—VARIATIONS WITH INDIVIDUALS ON THE SAME DIET.

Date, 1933.	Subject A.		Subject B.	
	Urine volume, cc.	Mg. As <i>per</i> <i>diem.</i>	Urine volume, cc.	Mg. As <i>per</i> <i>diem.</i>
4/5	1,475	0.11	1780	Less than 0.09
4/25	2,165	0.08	1845	Less than 0.10
4/26	2,225	0.34	1925	0.14
4/27	2,185	0.25	1500	0.23
5/7	1,220	0.04	1490	0.15
	<hr/> 10,270	<hr/> 0.82	<hr/> 8540	<hr/> 0.52+
1935.	Subject C.		Subject D.	
1/31	1295	0.30	415	0.15
2/1	1860	0.69	2700	1.13
2/2	4570	2.40	2290	0.78
2/3	1420	0.22	2000	0.45
	<hr/> 9145	<hr/> 3.61	<hr/> 7405	<hr/> 2.51

Discussion. Considerable controversy exists over the term "normal arsenic." The frequent occurrence of traces of the metal in normal tissues is no longer a debatable question, but it has never been demonstrated that arsenic is essential for normal tissue function. Its presence, therefore, is to be regarded as accidental. It is immaterial, from the standpoint of urinary concentration, whether this arsenic is designated as normal or subclinical.

Boos and Werby¹ support the contention that there is no such thing as normal arsenic in forensic medicine. They advocate using gross methods and selecting samples small enough to render normal specimens invariably negative. No one can question this practice as applied to cadavers in legal medicine, but the clinician is interested chiefly in those amounts of arsenic which can be ignored by the toxicologist. Had we taken 5 cc. of urine for oxidation and 2 cc. for electrolysis, all specimens containing less than 0.25 mg. As per liter would have been reported as negative. On the other hand, had we analyzed large enough samples, all would have been found to be "positive." The necessity for a standardized procedure which will detect physiologically important amounts of arsenic in the urine is obvious. The method of sampling suggested by the authors is practical and clinically useful.

The literature is deluged with papers ascribing any number of pathologic states to chronic arsenic intoxication. Unfortunately these contentions are usually based upon assumptions rather than upon acceptable arsenic determinations under controlled conditions. For example, 69 out of 100 patients with biliary tract disease were said to have excreta (mainly urine) "positive for arsenic," but no figures were given nor controls studied. This was reported as evidence for the arsenical etiology of the observed hepatitis. A comparable series of perfectly normal individuals would undoubtedly have shown the same urinary arsenic values.

The ultimate effect of long exposure to dietary and cosmetic arsenic is still a matter of conjecture. It is desirable, however, that the clinician be enabled by laboratory analyses to ascertain the rôle played by arsenic in his patients. As conducted at present, the vast majority of determinations are entirely misleading.

It has been our aim to provide a fundamental control diet to permit further study of the behavior of arsenic in the body. Investigations are under way to achieve a diet which will be somewhat more varied. When sufficient data have been assembled, it will be feasible to add known amounts of arsenical compounds to this standard diet for the purpose of ascertaining the degree of retention of the metal in persons suspected of chronic poisoning or hypersensitivity. The effect of popular therapeutic agents must be studied in the same fashion.

Summary. 1. Satisfactory studies of urinary arsenic excretion cannot be made on casual specimens.

2. The urinary arsenic excretion of normal individuals on an average diet fluctuates from day to day over a wide range; in our subjects (163) from negative (18%) to 0.85 mg. of arsenic (As) *per diem* with the mean at 0.26 mg.

3. Figures for urinary arsenic excretion have no meaning unless the diet is known.

4. An arsenic-low diet is suggested which decreased the urinary elimination in 48 subjects; they ranged from negative (62%) to 0.2 mg. arsenic (As) *per diem* with the mean at 0.07 mg.

5. Results of studies of urinary arsenic excretion can be interpreted only in the light of a standardized chemical procedure for the detection of arsenic.

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URINARY EXCRETION OF ARSENIC.

II. THE INFLUENCE OF THIOSULPHATE.

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It is the accepted practice among clinicians to treat persons suspected of chronic arsenical poisoning with a course of thiosulphate injections. This is usually done prior to the collection of urine specimens for analysis. Cannon¹ almost invariably found that patients who had dermatoses and low blood arsenic values on admission reacted to sodium or calcium thiosulphate therapy with a temporary rise in both blood and urine arsenic. This was taken as suggesting a mobilization of the metal from internal storage depots followed by excretion. Although Cannon used thiosulphate both intravenously and orally on a great number of patients with apparent clinical benefit, he undoubtedly presents opinions rather than statistical data. Despite the fact that Cannon recognized the dietary source of body arsenic, he apparently failed to consider it in interpreting his analyses.

Kuhn and Reese² believed that their experimental results indicated that thiosulphate increased the urinary arsenic output. Young³ found that sodium thiosulphate diminished the rate of arsenic excretion, although clinical improvement was concomitant with the therapy.

The attention of one of us (M. R. M.) was attracted several years ago to the consistently low urinary arsenic values of dermatologic patients who had received 3 injections of thiosulphate at 48-hour intervals before collecting the 24-hour test specimens.

Materials and Methods. Thiosulphate is used so extensively as a therapeutic agent that no lack of uncontrolled material was at hand. Where, however, the dietary intake of arsenic is not known, the urinary arsenic values following injection of thiosulphate are meaningless, as is indicated in Paper I.³ If thiosulphate mobilizes arsenic for excretion, it should have been easy to demonstrate it on individuals limited to an arsenic-low diet for several days prior to and during the course of the injections. Since a single specimen may have been invalidated by chance arsenic in the food, it was considered advisable to perform the analyses for a 3- to 7-day period. The necessity for using only freshly prepared solutions of thiosulphate was recognized. The experiments were restricted to intravenous administration of the therapeutic agent.

The diets and the analytical procedures were those previously described.³

Results and Discussion. Table 1 presents the findings in a neurological patient (courtesy of Dr. George Blakeslee) whose symptoms were thought to be due to a chronic arsenical poisoning acquired from food, beverages, or tobacco. The patient was placed upon a diet which, except for breadstuffs, was regarded as arsenic low. The results were slightly higher than anticipated from the diet during the 5 control days. Thiosulphate was administered daily at noon for 6 days subsequently. A strict record was kept of the diet throughout, the patient cooperating enthusiastically and intelligently. The evidence points to a suppression of arsenic excretion.

TABLE 1.—EFFECT OF THIOSULPHATE UPON URINARY ARSENIC EXCRETION.

Date, 1935.	Urine volume, cc.	Arsenic (As).		Remarks.
		Mg. per 100 cc.	Mg. per diem.	
9/24	850	0.04	0.34	Subject on restricted diet.
9/25	645	0.04	0.26	
9/26	705	0.03	0.21	
9/27	600	0.03	0.18	
9/28	525	0.04	0.22	
10/2	505	0.015	0.08	Diet continued; sodium thiosulphate administered daily by injection. Last thiosulphate injection.
10/3	550	0.015	0.08	
10/4	1295	0.007	0.09	
10/5	600	Negative	Less than 0.03	
10/6	805	Negative	Less than 0.04	
10/7	920	0.007	0.06	
10/8	1300	v. f. t.	Less than 0.1	
10/9	595	0.023	0.14	

In Table 2 are outlined the results obtained with a patient (courtesy of Dr. Wilbur Duryee) admitted to the Vascular Clinic for study for a condition in which arsenic has been reported as hav-

TABLE 2.—EFFECT OF THIOSULPHATE UPON URINARY ARSENIC EXCRETION.

Date, 1935-36.	Urine volume, cc.	Arsenic (As).		Remarks.
		Mg. per 100 cc.	Mg. per diem.	
12/20	680	0.023	0.16	Regular diet.
12/21	670	0.038	0.25	
12/22	1000	0.015	0.45	
		Av. 0.28		
1/12	575	0.023	0.13	Restricted diet.
1/13	550	0.015	0.08	
1/15	760	0.045	0.34	
		Av. 0.18		
1/18	365	0.053	0.19	Restricted diet with daily injections of thiosulphate.
1/19	740	0.023	0.17	
1/20	590	0.015	0.09	
		Av. 0.12		

ing etiologic significance. This patient found the restricted diet very distasteful, but she attempted to follow it as well as she could under her home conditions. The thiosulphate had little effect upon the arsenic excretion, but the tendency was toward a diminished output.

The data in Table 3 were secured during the experimental determination of an arsenic-low diet. Analyses before and after the thiosulphate demonstrate no appreciable mobilization of arsenic for excretion.

TABLE 3.—ARSENIC EXCRETION UNDER THE INFLUENCE OF THIOSULPHATE.

Date, 1935.	Urine volume, cc.	Arsenic (As).		Remarks.
		Mg./100 cc.	Mg./volume.	
1/31 . .	1295	0.022	0.29	
2/3 . .	1420	0.015	0.21	
2/6 . .	1550	0.026	0.40	
2/7 . .	1800	0.019	0.34	
2/8 . .	7 A.M.—10 A.M. 350	0.010	0.04	Thiosulphate given intra- venously at 10 A.M.
	10 A.M.—7 P.M. 600	0.007	0.04	
	7 P.M.—7 A.M. 875	0.004	0.04	
2/9 . .	7 A.M.—7 P.M. 860	0.015	0.13	
	7 P.M.—7 A.M. 1300	0.022	0.28	
2/10 . .	2790	Trace	Less than 0.15	
2/11 . .	2255	0.007	0.16	
2/12 . .	2050	0.007	0.14	

TABLE 4.—ARSENIC EXCRETION UNDER VARIOUS CONDITIONS.

Date, 1936.	Urine volume, cc.	Arsenic (As).		Remarks.
		Mg. per 100 cc	Mg. per diem.	
2/20 . .	1150	0.022	0.25	Light diet with "Titro" salt.
2/24 . .	1005	0.022	0.22	Na ₂ S ₂ O ₃ intravenously.
2/25 . .	725	0.019	0.13	Na ₂ S ₂ O ₃ intravenously.
2/26 . .	865	0.045	0.39	
2/27 . .	1055	0.015	0.16	Beginning of arsenic- low diet.
2/29 . .	450	0.022	0.09	Na ₂ S ₂ O ₃ intravenously.
3/1 . .	325	0.015	0.05	
3/3 . .	480	0.010	0.05	
3/4 . .	825	0.022	0.18	
3/5 . .	850	0.015	0.13	Last day of calamine lotion.
3/6 . .	945	0.007	0.06	
3/9 . .	985	Negative	Less than 0.05	CaS ₂ O ₃ intravenously.
3/10 . .	800	Negative	Less than 0.04	CaS ₂ O ₃ intravenously.

The patient followed in Table 4 was admitted to the hospital on the dermatologic service (courtesy of Dr. Laird Van Dyck) and subjected to local treatment involving several agents known to contain appreciable amounts of arsenic. Since it was regarded that gross contamination of the urine with ointments or lotions was unlikely, the arsenic excretion was assumed to be dependent upon that absorbed through the skin and ingested with the food. There is no apparent evidence that thiosulphate increased the elimination of arsenic.

Summary. 1. It is possible to study the effect of thiosulphate upon the excretion of arsenic only under conditions which control the ingestion of arsenic.

2. Thiosulphate administered intravenously does not increase the urinary elimination of arsenic but tends to diminish it, not only on the day of injection but subsequently.

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THE PRESENT STATUS OF THE PREVENTION AND TREATMENT OF INFLUENZA.*

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CLINICIANS are inquiring for information concerning specific preventive and therapeutic agents for combating influenza. Briefly the story follows:

In 1931, Dr. Richard E. Shope reported that swine influenza, a severe respiratory disease which was first noticed in 1918 in Iowa at the time of the human influenza epidemic, was caused by a filtrable virus plus a bacillus, *H. influenzae-suis*. The virus alone produced a mild respiratory disease. Intramuscular injection of the virus alone conferred immunity in swine; whereas intramuscular injection of *H. influenzae-suis* gave no immunity to the virus disease, but protected them to some extent from the more severe manifestations of the disease, due to the concerted action of the virus and the bacillus.

In 1933, Smith, Andrewes and Laidlaw, in England, were able to infect ferrets with filtered nasal washings from a man ill with epidemic influenza. The severe disease could be transmitted from ferret to ferret without the synergistic activity of bacteria. Further work showed that Shope's swine influenza virus caused a disease in ferrets identical with that caused by the human virus. Moreover, Shope demonstrated that if the instillation of virus into the nares of ferrets was accompanied by ether anesthesia, pneumonic lung lesions developed. This method also produced a fatal pneumonia in mice with both viruses.

* This article was kindly prepared by the authors at our request, to satisfy enquiries that had been received from physicians in regions where influenza is now epidemic.
—THE EDITORS.

A strain of human influenza virus (*PR* 8) was isolated by Dr. Thomas Francis, Jr., from the epidemic in Puerto Rico of 1934. Since then human viruses have been isolated by Dr. Francis from washings obtained in Point Barrow, Alaska, and from Philadelphia and New York. Isolation of a similar virus was made by Dr. F. M. Burnet working in Australia. These viruses from human cases have been found to be immunologically identical. Convalescent sera obtained from various points throughout the world have been found to contain protective antibodies, so that a mixture of virus and serum fails to infect experimental animals. Some of these sera were preserved in the dried form by the Flosdorf-Mudd method. Convalescent serum has proven of value in the treatment of mice infected with influenza virus. No data are available as yet, however, concerning its advantages in the treatment of human beings.

A ferret recovered from the virus disease is immune for a number of months. If after that it receives a subcutaneous dose of active virus (inactive virus does not suffice), its immunity returns. Intradermal, subcutaneous, intramuscular, intraperitoneal, and intravenous injections of the active virus did not produce the disease in animals. Human beings have already been injected subcutaneously and intramuscularly with active virus for the production of immunity and although neutralizing antibodies to the human virus are increased thereby, it is not yet known if such inoculations protect. So much for the scientific aspects of influenza. Now let us turn to a practical consideration of the disease.

When the physician is called to a houseful of patients, he still must rely upon his own experience or the general treatment recommended in current standard textbooks of medicine to guide him in handling his problem. He knows that uncomplicated influenza is a mild febrile disease lasting 4 or 5 days and leaving the patient weak out of all proportion to the activity of the acute stage. He knows that complications are frequent, severe, disabling and often fatal. Therefore, he bases the logic of his measures upon this foundation. The patient must be put to bed as early as possible and kept there until at least 48 hours after he has become afebrile. Diet should be entirely liquid, being a total of 2000 to 3000 cc. per day for adults, given in small amounts and frequently during the height of the illness. Soft food should be given on or about the fourth day, followed by a slow return to the normal diet. A small enema is preferred to laxatives. Cathartics should be avoided. The patient should have absolute rest with his head and shoulders slightly elevated. The cough should be treated by methods designed to make the sputum liquid and therefore more easily expectorated, rather than by methods designed to suppress the cough. Aches and pains may be modified by the judicious use of acetylsalicylic acid or by other analgesics, but excessive sweating is dangerous. Pneumonia is the chief complication to be avoided;

other complications are meningitis, encephalitis, pleurisy, bronchitis, otitis and nephritis. Good nursing is the best method of staving off complications.

If possible, the patient should be isolated not only for the protection of others, but also for his own protection. Visitors should not be allowed during the acute stage.

The herding together of influenza patients in hospital wards is to be avoided on account of the probable spread of secondarily invading bacteria. If reasonable isolation, complete rest and good care are available at home, patients should not be moved.

An excellent summary of our present knowledge of the etiology of influenza is to be found in "Studies in Influenza," by Dr. Thomas Francis, Jr., of the Rockefeller Foundation (*Penna. Med. J.*, 40, 249, 1937). For those who are interested in delving into the literature, the following papers are suggested:

FRANCIS, T., JR.: Recent Advances in the Study of Influenza, *J. Am. Med. Assn.*, 105, 251, 1935.

FRANCIS, T., JR., and MAGILL, T. P.: The Incidence of Neutralizing Antibodies for Human Influenza in the Serum of Human Individuals of Different Ages, *J. Exp. Med.*, 63, 655, 1936.

FRANCIS, T., JR., and MAGILL, T. P.: The Antibody Response of Human Subjects Vaccinated with the Virus of Human Influenza, *J. Exp. Med.*, 65, 251, 1937; also *Proc. Soc. Exp. Biol. and Med.*, 33, 604, 1935-36.

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SHOPE, R. E.: The Incidence of Neutralizing Antibodies for Swine Influenza Virus in the Sera of Human Beings of Different Ages, *J. Exp. Med.*, 63, 669, 1936.

BRIGHTMAN, I. J., and TRESK, J. D.: Recovery of Filtrable Virus from Children with Influenza. Epidemiologic and Clinical Observations, *Am. J. Dis. Child.*, 52, 1, 1936.

WELLS, W. F., and BROWN, H. W.: Recovery of Influenza Virus Suspended in Air and Its Destruction by Ultraviolet Radiation, *Am. J. Hyg.*, 25, 227, 1936.

In summary, we may say that progress is being made in the specific knowledge of influenza, so that effective methods of immunization and treatment may be available in the near future. At present the physician must treat his patients symptomatically with the object of preventing complications and he should do this by the gentle but persistent means of rest in bed, a glass of fluid every hour, mild enemas instead of strong purgatives, analgesics and sedatives in moderation, the best nursing obtainable, and the isolation of the patient. It is better to do too little than too much in the way of dosing with drugs.

BOOK REVIEWS AND NOTICES.

ANATOMY OF THE HUMAN BODY. By HENRY GRAY, F.R.S., Fellow of the Royal College of Surgeons; Lecturer on Anatomy at St. George's Hospital Medical School, London. Pp. 1381; 1216 illustrations. Twenty-third edition, thoroughly revised and re-edited by WARREN H. LEWIS, B.S., M.D., Professor of Physiological Anatomy, Johns Hopkins University, Baltimore, Maryland; Research Associate, Carnegie Institution of Washington. Philadelphia: Lea & Febiger, 1936. Price, \$10.00.

"SINCE the publication of the first English edition of this work in 1858 and the first American edition in 1859 great advances in the subject of Anatomy have been made, especially in microscopic anatomy and the anatomy of the embryo. This knowledge was embodied from time to time in the successive editions until finally considerable portions of the text, sometimes sections, were devoted to these subjects. However, the main text has always remained primarily a descriptive anatomy of the human body. The distribution of the special sections on embryology and histology among the subjects with which they naturally belong has been retained in the present edition. Such an arrangement serves to emphasize the unity of the three great divisions of human anatomy, namely—embryology, microscopic anatomy and gross anatomy—and the advantage of their coördinate study for the best understanding of the structure of the human body. In addition to the endeavor to bring each section up to date by incorporating new knowledge which has appeared since the previous edition, the sections on embryology, the central nervous system, and the ductless glands have been thoroughly revised and new material has been added on the physiological anatomy of various organs. . . . New illustrations have been added and many old ones have been replaced by more effective figures. . . . The use of the B.N.A. nomenclature in English has been retained practically unchanged in this edition except for the adoption of Langley's terminology of the autonomic nervous system. Important references to the literature have been added at the end of each section. . . . It is interesting to note that although Henry Gray saw only the first edition, much of the original text persists and many of his illustrations are still in use." (Editor's Preface).

THE PHENOMENA OF LIFE. A Radio-electric Interpretation. By GEORGE CRILE. Edited by AMY ROWLAND. Pp. 379; 113 illustrations and 22 tables. New York: W. W. Norton & Co., Inc., 1936. Price, \$3.50.

THE dangers of a *post hoc ergo propter hoc* type of reasoning are well exemplified in this, the most recent of the author's works. The observation that living tissues possess electrical properties was made as far back as the 18th century. The author, rediscovering this fact, has noted, in a series of experiments, the influence of various chemical, physical and operative procedures upon these electrical phenomena. The central thesis of this book appears to be the radio-electric theory of life processes, which, in the words of the author, postulates that living organisms are bipolar mechanisms constructed and motivated by radiant and electrical forces.

It is evident that the book represents extensive reading in many fields. However, there is apparent throughout a definite tendency to emphasize those investigations of other workers which lend support to the hypotheses of the author. The style of writing is free and flowing, and both material and argument are presented in an interesting fashion. While an endeavor

is made throughout to maintain a scientific tone, the note at times becomes somewhat metaphysical. Too many postulates and assumptions are made and bolstered up with miscellaneous data, references and dubious experiments. For instance, it is unfortunate that the author has attached so much significance to minor cytologic changes. The use of dead tissue without an adequate consideration of the factor of postmortem change is fraught with great danger. Notwithstanding all of this, the work is stimulating, and can be recommended even to those who do not agree with the theories of the author.

H. D.

THE TOXÆMIAS OF PREGNANCY. By DAME LOUISE McILROY, D.B.E., LL.D., M.D., D.Sc. (GLASG.), D.Sc. (LOND.), D.Sc. HON. (BELFAST), F.C.O.G., M.R.C.P., Consulting Obstetrician and Gynecological Surgeon, Royal Free Hospital; Surgeon, Marie Curie Hospital, etc. Pp. 355; 19 illustrations. Baltimore: William Wood & Co., 1936. Price, \$5.00.

THIS ill-defined symptom complex is comprehensively reviewed and the many problems encountered in its prevention and treatment thoroughly discussed. The findings and opinions from every country are presented, with the exception that German literature seems incompletely covered.

The book takes up the statistical aspect of the subject stressing maternal and fetal mortality, then covers the theories and classifications and follows with the functional studies of the normal and abnormal pregnancy. Antenatal care is exhaustively studied under the subject of nutrition, diet deficiency and relation of weight changes of toxemias.

The authoress regards the theories and classification as still incomplete and poorly founded. She suggests further research on the endocrine aspect and deficiency theories of this condition. The symptoms and signs of toxemia she feels are mostly effects of altered metabolism and represent increasing recessions of defense.

Chronic nephritis in pregnancy is considered as an entity and forms the subject of a very able section, as does also the contribution of her co-worker, Jane McIlroy, on the eye changes of toxemia. The authoress emphasizes the importance of antenatal care and prophylaxis and stresses conservative medical treatment with a minimum of obstetric interference.

P. W.

A MANUAL OF PRACTICAL OBSTETRICS. By O'DONEL BROWNE, M.B., B.Ch., B.A.O., F.R.C.P.I., L.M. (ROTUNDA HOSP.), M.C.O.G., Assistant Gynecologist, Sir Patrick Dun's Hospital, Dublin; Assistant to the Professor of Midwifery, Trinity College, Dublin. Pp. 363; 236 illustrations and 10 plates, some in color. Baltimore: William Wood & Co., 1936. Price, \$6.50.

THIS book has been written to present the subject of Clinical Obstetrics in as practical a form as possible. It is felt that the author has succeeded very well in his effort. He has left out statistics and theoretical considerations largely and has expressed very definitely his own views and methods of handling difficult situations. The illustrations which are borrowed in part from other works serve well to illustrate the text.

Anatomy and Physiology are briefly discussed. Antenatal care is gone into in much detail, here as in other sections of the book there seems to be a considerable tendency to recommend proprietary medicines by name. In discussing the diseases complicating pregnancy the author does not mention the use of early Cesarean section in diabetes, a procedure which is often used in this condition in the United States. The directions for the conduct of pregnancy, obstetrical diagnosis, mechanism and conduct of normal labor, care of the patient during labor are gone into thoroughly,

simply, and concisely with practical suggestions. The lateral position suggested is not in use in the United States and the frequent interspersing of illustrations of patients in the dorsal with those of patients in lateral positions is confusing. The author does not favor rectal examinations in labor.

A rather marked error in proofreading occurs on page 66: "Sometimes it is more convenient to remove the baby before stitching a torn perineum." In the able chapter on Stimulants and Anesthetics of Labor, the barbiturates are not mentioned. Follow-up examination over a sufficient period of time is stressed in the care of the puerperal patient. The abnormalities of labor, hemorrhages and the treatment of various complications are well presented. The author evidently feels that Cesarean has not been employed in sufficient frequency in Ireland for placenta previa. The Rotunda method of treating convulsive toxemias of pregnancy is the author's choice. The Strogino treatment is also described. There is a fine chapter on Puerperal Sepsis.

The book concludes with three chapters written by colleagues, one on the Newborn Infant by Collis, which is a fine presentation, a chapter on Radiology written by McDonogh, which stresses the importance of Roentgen ray examinations in obstetrical practice and a concluding discussion of Blood Typing and Blood Transfusions by Dockeray.

This is an excellent presentation of practical obstetrics, a working manual, eminently suitable for the general practitioner. P. W.

A DIABETIC MANUAL. For Practitioners and Patients. By EDWARD L. BORZ, A.B., M.D., F.A.C.P., Associate Professor of Medicine, Graduate School of Medicine, University of Pennsylvania; Chief of Medical Service B, The Lankenau Hospital, Philadelphia, etc. With a Foreword by GEORGE MORRIS PIERSOL, B.S., M.D., F.A.C.P., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, etc. Pp. 222; 12 illustrations (2 in color). Philadelphia: F. A. Davis Company, 1936. Price, \$2.00.

A DIABETIC manual today may be likened to a new recruit to the campaign for medical education. For the patient, this book offers a thoroughly sound and reliable presentation of diabetes and its care in very clear language. Chapters on the teeth, feet, juvenile diabetes and surgery by contributing authors have added to this elementary book as they do to texts. The section on Protamine Insulin is very wisely written in view of its recent introduction.

There should be more equivalents or substitutes in the protein and fat foods, and the 3-page table of the sodium chloride content of foods seems unnecessary in connection with hypertension, since medical authorities are not in agreement on the value of salt restriction in this condition. Such comments are minor points. The manual lacks the encouragement on every page, the optimistic enthusiasm which may be needed to encourage an ignorant first reader. This may prove to be an advantage in not obscuring the facts of diabetes and details of its care. In any case, the manual should rank very high and have a useful part in promoting the proper management of diabetes. F. L.

THE THEORY AND PRACTICE OF PSYCHIATRY. By WILLIAM S. SADLER, M.D., Chief Psychiatrist and Director, The Chicago Institute of Research and Diagnosis; Consulting Psychiatrist to Columbus Hospital, etc. Pp. 1231. St. Louis: The C. V. Mosby Company, 1936. Price, \$10.00.

This encyclopedic volume, with topics ranging from infancy to senescence, expresses the author's extramural, psychiatric viewpoint, and, as

such, is probably without an equal in any language. Here is offered a valuable reference work to psychiatrists, general practitioners, teachers, ministers, social workers and psychologists.

The subject matter is considered as the Theory of Psychiatry, Personality Problems, The Neuroses, The Psychoses and Psychotherapeutics. The thoroughness with which these parts are discussed is suggested by the list of headings under Personality Problems: What is Personality? Classifications of Personality, Unification of Personality, Maladjustments of Personality, Technics of Adjustment, Personality of the Nursery, Childhood Psychology, Personality of the Preschool Child, Play, Education and Discipline. Preadolescence and Adolescent Difficulties, The Adolescent Personality, Adolescent Personality Problems, Family Relationships, and Problems of Adult Personality.

Perhaps there is a tendency to dogmatize too strongly on some moot problems as may be shown in the discussion of sterilization: "There is no question that a sterilization law, enforced throughout the United States, would result, in less than one hundred years, in eliminating a large amount of crime, insanity, feeble-mindedness, moronism and abnormal sexuality, as well as many other forms of defectiveness and degeneracy." This is not in accord with our best thought, where it appears sterilization should only be done with the consent of the individual or those responsible for him, thus obviating possible constitutional, religious and other objections.

Back in the 6th century, the famed Gheel colony method of caring for those mentally afflicted, had origin, and its inclusion here would have been most appropriate to the general design of the author. Within the environs of this Belgian town are at present about 2500 selected patients who are boarded out amongst the townfolks. The advantages thus afforded are those of home comfort, freedom and occupation; and all provided at a lessened expense to the taxpayer. It is said that locally the social standing of the hosts is determined by the care bestowed upon those committed to their custody.

Features of the book worthy of commendation are clarity of presentation, an abundant and revealing bibliography at the end of each chapter, a glossary of 34 pages and an index of 36 pages.

N. Y.

THE OPERATIONS OF SURGERY. Vol. 1. The Upper Extremity, The Head and Neck, The Thorax, The Lower Extremity, The Vertebral Column. By R. P. ROWLANDS, M.S. (LOND.), F.R.C.S. (ENG.), Late Surgeon to Guy's Hospital; Late Lecturer on Surgery to the Medical School; and PHILIP TURNER, B.Sc., M.S. (LOND.), F.R.C.S. (ENG.), Consulting Surgeon to Guy's Hospital; Formerly Lecturer on Surgery and Teacher of Operative Surgery to the Medical School. Pp. 1043; 435 illustrations, 38 in color. Eighth edition. Baltimore: William Wood & Co., 1936. Price, \$10.00.

THIS 8th edition, published after the death of Mr. Rowlands, was revised by him in many of the chapters; the rest of the revision was done by Messrs. W. H. Ogilvie, Grant Massie, and A. R. Thompson. This book, as in previous editions, gives a detailed account of the standard operations of surgery and a fair criticism of newer methods is inserted. In addition to the operations in common surgery there are sections on otology, laryngology, gynecology, orthopedics and neurosurgery. In this volume general chapters are given on the examination and preparation of the patient for operation and postoperative treatment. The various operations of the above-named parts are detailed with many illustrations, some of which are in color. The book is of the same type as in previous editions and represents a well-known standard text on surgical operations brought up to date.

L. F.

MEDIZINISCHE PRAXIS. Sammlung für Ärztliche Fortbildung. Edited by PROFESSORS L. R. CROTE, A. FROMME and K. WARNEKROS. Dresden: THEODOR STEINKOPFF, 1936. *Band XX. Diätetik.* Die Ernährung des Gesunden und des Kranken. By PRIVATDOZENT DR. WILHELM HEUPE, Oberarzt an der Medizinischen Universitäts-Poliklinik, Frankfurt A.M. Pp. 192. Price: Paper, Rm. 9.50; Bound, Rm. 10.80. *Band IX. Blutung und Fluor.* By PROFESSOR DR. HANS RUNGE, Direktor der Universitäts-Frauenklinik Heidelberg. Pp. 117; 18 illustrations. Second edition. Price: Paper, Rm. 7; Bound, Rm. 8.

FROM time to time there have appeared in this Series short monographs in various medical fields, notably those to which recent and significant advances have lent particular interest. The monographs have been written especially with the viewpoint and need of the general practitioner in mind. The books are of a convenient size, containing from 80 to 220 pages, and are available in paper or more substantial bindings at prices ranging from Rm. 4.50 to Rm. 16.00. Of the two volumes here considered, the one on dietetics, recently issued, is a practical discussion of nutrition and feeding in health and disease. In its comparatively small compass it nevertheless covers the subject unusually well, with only one disadvantage for American readers, in that it speaks in terms of German cooking. The other volume, now in its second edition, considers the gynecologic topics of menstruation, bleeding and discharge. It is a splendid presentation, particularly as concerns present knowledge of endocrine functions. Both books fully qualify under the subtitle of this Series, "Collection for Postgraduate Education of Physicians," and are warmly recommended to all practitioners who read German.

R. K.

DIE WERKE DES HIPPOKRATES. HERAUSGEGEBEN VON DR. MED. RICHARD KAPFERER unter MITWIRKUNG VON PROF. DR. GEORG STRICKER, Würzburg. Book 10: Die Krisen; Die Kritischen Tage; Prognostikon—(The Crises); (The Critical Days); (The Prognostics). Pp. 75. Stuttgart: Hippokrates Verlag G.M.B.H., 1936. Price, Rm. 5.25. (To be published in 25 parts costing ca. Rm. 100, card binding.)

RECOGNIZING that the two works, "Crises" and "Critical Days," are generally not included in the Hippocratic corpus, as they are not mentioned by Erotian or Galen, the Editor of this edition nevertheless includes them as he finds internal evidence suggesting that they were formerly included in "Diet in Acute Diseases." "Prognostikon," generally accepted as a true work of Hippocrates, gives a matchless exposition of this important part of the Hippocratic art. After pointing out the importance of being able to predict the patient's future from knowledge of his past and present condition, the author points out what may be learned from the expression of the face (here we find the *facies Hippocratica*), the position in bed, the hands (*carphalugia*), the respiration, sputum, urine, feces and so on, ending with a consideration of the effect of the Macrocosm (airs, miasma, seasons) on the sick individual.

E. K.

MICROBIOLOGY AND PATHOLOGY FOR NURSES. By CHARLES F. CARTER, B.S., M.D., Director, Carter's Clinical Laboratory, Dallas, Texas; Formerly Director of Laboratories, Parkland Hospital, Dallas, and Lecturer in Bacteriology and Pathology, Parkland Hospital School of Nursing. Pp. 682; 138 illustrations and 14 color plates. St. Louis: The C. V. Mosby Company, 1936. Price, \$3.00.

THE material is presented simply and lucidly, avoiding controversial points; the survey of the subject, however, is rather exhaustive, encompassing a greater scope than the usual nursing class could grasp in the time allotted for this subject. As a reference book for the nurse on any particu-

lar case, it provides much practical information to increase her interest, orient her thoughts, and improve her professional care. As an easily readable survey, its perusal by the physician would recall many practical points apt to be overlooked in the minutiae of medical school classes. The chapters are supplemented by relevant laboratory exhibits, review questions and brief bibliographies of pertinent references among other textbooks. A glossary of some 800 words and a good index conclude the book.

O. S.

THE SURGICAL CLINICS OF NORTH AMERICA. VOL. 16. No. 3 (NEW YORK NUMBER—JUNE, 1936). Pp. 277; 79 illustrations. Philadelphia: W. B. Saunders Company, 1936. Price: Paper, \$12; Cloth, \$16. (Per Clinic Year, February to December.)

OF the 22 items of this New York number the first four constitute a small symposium on surgery for pain. Among the interesting articles noted are two on the parathyroids by Garlock and Parsons; Dudley's discussion of splenectomy and hemolytic jaundice, in the second case of which—one of active syphilis—the removed spleen was found to contain numerous spirochetes; and Farnham's borderline topic of "Cardiac Disorders in Surgical Patients." An Index for the three numbers of Volume 16 is included.

E. K.

TISSUE IMMUNITY. By REUBEN L. KAHN, M.S., D.Sc., Assistant Professor of Clinical Bacteriology and Serology, and Director of Clinical Laboratories at the University Hospital, Ann Arbor, Mich. Pp. 707; illustrated. Springfield: Charles C Thomas, 1936. Price, \$7.50.

THIS is the first attempt at presenting the broad subject of immunity from the angle of tissue immunity. Naturally, then, many new views are presented which are an elaboration of the theories presented by the author at various scientific meetings during the last 4 years. These new viewpoints should be of interest to the clinician, the pathologist, the bacteriologist, the dermatologist, and others, as well as to the teacher and student of immunology. The mass of data presented is based on quantitative studies conducted by the author and his corps of assistants. Practically every chapter closes with a section dealing with the consideration of the clinical applications of the material presented.

H. M.

GYNECOLOGY AND OBSTETRICS. (Vol. XVII of *Clio Medica*). By EDWIN M. JAMESON, M.D., Surgeon, General Hospital; Consulting Surgeon, Reception Hospital, Saranac Lake, N. Y. Pp. 170; 5 illustrations. New York: Paul B. Hoeber, Inc., 1936. Price, \$2.00.

DR. JAMESON has given us a delightfully written account of the early customs and manners in obstetric practice and teaching, as well as depicting the rise of the recent speciality of gynecology, in this newest example of the series on the history of medicine which have been appearing under the title of *Clio Medica*.

Evidently in obstetrics as in other branches of science little that we think is new is really new; for, as the author carries us through the traditions and customs of the early period and those of the Greek and Roman period, we find many suggestive allusions to methods which are not far different from those of the present day. What a commentary it is on the profuse output of the obstetrical and gynecological texts of this era to read that the famous "Rosengarten" of Eucharius Röslein was the first obstetric textbook to be issued in fourteen centuries. Reviewers must have had an easy time in those days.

The Modern period of obstetrics begins with the work of Mauriceau, van Deventer, and Portal and from this we are carried on to the development of obstetrical teaching in the modern manner and to the development of the modern maternity hospital. One of the most interesting chapters in the book is the account of the Chamberlein family and the development of the obstetric forceps. The story of puerperal fever is no less interesting, especially in view of the fact that sepsis still remains the scourge of modern maternity. It is especially pleasing to note the large part which American surgeons took in the development of gynecological technique. The obstetrical classics; in many instances records of the original procedures and discoveries. This most interesting contribution to the history of obstetrics and gynecology deserves to be widely read.

P. W.

STARLING'S PRINCIPLES OF HUMAN PHYSIOLOGY. Seventh Edition, edited and revised by C. LOVATT EVANS, D.Sc., F.R.C.P., F.R.S., LL.D., B'ham., Jodrell Professor of Physiology in University College, London. The Chapters on the Central Nervous System and Sense Organs Revised by H. HARTRIDGE, M.A., M.D., Sc.D., F.R.S., Professor of Physiology at St. Bartholomew's Medical College. Pp. 1096; 554 illustrations (6 in color). Philadelphia: Lea & Febiger, 1936. Price, \$8.75.

"THE revelation of the structure of some of the vitamins, the advances in the chemistry of the hormones, particularly the sex hormones, in the chemistry of the carriage of carbon dioxide in the blood and of the humoral transmission of nervous impulses, have all received the consideration to which their importance entitles them. The advances in experimental physiology and biophysics likewise have demanded a thorough revision of the text and the methods for the recording of nervous impulses and for the study of the reproductive cycle have both been included. Practically every chapter has been revised to embrace these features and many sections have been rewritten. On the other hand, there has been such a careful pruning and elimination of obsolescent matter that the size of the text has been somewhat reduced. The inclusion of references to current and to classic literature . . . has been retained in the form of foot-notes and in lists of general nature at the end of sections or chapters, thus enabling the advanced student to extend his reading." (From Publisher's statement.)

A TEXT-BOOK OF PHARMACOLOGY AND THERAPEUTICS or the Action of Drugs in Health and Disease. By ARTHUR R. CUSHNY, M.A., M.D., LL.D., F.R.S., Late Professor of Materia Medica and Pharmacology in the University of Edinburgh. Pp. 808; 70 illustrations. Eleventh edition, thoroughly revised by C. W. EDMUNDS, A.B., M.D., Professor of Materia Medica and Therapeutics and Director of the Pharmacological Laboratories in the University of Michigan, Ann Arbor, and J. A. GUNN, M.A., M.D., D.Sc., F.R.C.P., Professor of Pharmacology and Director of the Nuffield Institute for Medical Research, University of Oxford, Oxford, England. Philadelphia: Lea & Febiger, 1936. Price, \$6.50.

"THE appearance of the eleventh decennial revision of the Pharmacopœia of the United States has necessitated extensive changes, especially in the lists of official preparations. It has furnished an opportunity, not only to revise this classic work but make a very considerable rearrangement of its order. As in the previous edition, the successors of the distinguished original author have maintained the rigorously scientific and critical spirit that has made this book internationally famous. As a result, it has upheld its popularity with teachers and students.

In the first edition of this work, Cushny declared that the chief present function of pharmacology is destructive and critical. It still is, and worth-

less drugs continue to be dropped from the pharmacopœias. Constructive pharmacology is growing, however, and the extensive additions and alterations in this edition bear witness to its advances and to a growing interest in therapeutics. Every chapter has been modified and expanded and the entire book reset. The text reflects to an unusual degree the constructive mind and critical judgment of Dr. Cushny, the breadth and accuracy of his knowledge and his unswerving pursuit of truth that made him one of the most influential figures in the great advances of pharmacology. This edition is in every way worthy of him." (Publisher's statement.)

ARTHRITIS AND RHEUMATIC DISEASE. By MAURICE F. LAUTMAN, M.D., Consultant to the United States Public Health Service Clinic and Director of the Department for the Study of Arthritis, Levi Memorial Hospital, Hot Springs, Arkansas. With a foreword by MORRIS FISHBEIN, M.D. Pp. 177; 12 illustrations. New York: McGraw-Hill Book Company, Inc., 1936. Price, \$2.00.

This book the second volume in the "Whittlesey House Health Series," intended for the information of people without medical training, is simple in its language, sane and common-sense in its advice, and surprisingly complete in content. The author has been careful to present both, or several, sides of unsettled questions, and to indicate gaps in physicians' present knowledge of the disease. The emphasis is on early diagnosis, careful study, and early and persistent treatment. In the description of the "pre-arthritic stage," the stress on excessive fatigue as a symptom may be disturbing to a certain type of lay person. The Reviewer is inclined to think that the advantages of institutional or "resort" treatment are stated a trifle too strongly.

The typography and make-up of the book are good. The illustrations are poor, and contribute little; this is particularly true of the two Roentgen photographs.

The Reviewer believes that this book may, with profit, be prescribed for intelligent patients and patients' relatives, and he intends so to prescribe it.

J. C.

A TEXTBOOK OF HISTOLOGY. By JOSEPH KRAFKA, JR., Ph.D., M.D., Professor of Microscopic Anatomy, University of Georgia School of Medicine, Augusta. Pp. 246; 95 illustrations. Baltimore: The Williams & Wilkins Company, 1936. Price, \$2.50.

THIS is a condensed account of mammalian histology with frequent reference to contemporary viewpoints. It is intended for preliminary courses in the subject, and is expected to be supplemented by laboratory work. The illustrations are mostly diagrammatic and of a simplified character, in keeping with the purpose of the book.

W. A.

THE PRACTICE OF MEDICINE. By JONATHAN CAMPBELL MEAKINS, M.D., LL.D., Professor of Medicine and Director of the Department of Medicine, McGill University; Physician-in-Chief, Royal Victoria Hospital, Montreal, etc. Pp. 1343; 505 illustrations (35 in color). St. Louis: The C. V. Mosby Company, 1936. Price, \$10.00.

ALTHOUGH there are a number of good single volume textbooks of medicine on the market, another by a recognized authority is bound to have some value in emphasizing different points of view and bringing a certain freshness that is very difficult for a new edition of an old work to acquire. This book has the added advantage of an unusually large number of well

chosen and good illustrations, of which 35 are in color. The usual textbook paragraph on "Pathology" (meaning "Pathologic Anatomy") has properly been subordinated where material of more direct importance for the physician clamors for space. However, the lack of regularity that is evident in the book from several aspects is here manifest—in a quite unimportant way, to be sure—by the haphazard use of "Pathology," "Pathologic Anatomy" and "Anatomical changes" to indicate this section for the various diseases. The book includes a commendable number of recent advances, such as drug causation of agranulocytosis and its frequently hyperplastic marrow, the prostigmine treatment of myasthenia, modern views on Bright's disease, allergy (with a 7-page list of allergy-producing substances), radiation sickness, protamine insulinate, aleukemic reticulosis, to mention but a few of the many noticed by the Reviewer. The sections on diabetes mellitus and on the pituitary seem especially strong. It may be ungracious, then, to criticize apparent errors and omissions; but one must remember that there is already an abundance of good textbooks on this subject. Differences of opinion on medical problems are, of course, inevitable and the responsibility for typographical errors may be hard to fix. However, they are too numerous here to be passed without comment. "Pellagarsins" and "Chochin-China" (p. 734), "tarbardillo" (pp. 1193 and 1339), "maturation" (p. 532) are but a few of the errors found on a casual survey; while others like "destructive" for "distinctive" (p. 54), "as is" for "and is" (p. 55) cause an annoying waste of the reader's time in making out the true meaning. More important, and yet more open to difference of opinion, are such points as the omission of protein edema from the discussion of chronic malnutrition; of vitamin deficiency as a factor in alcoholic neuritis; of the hemopoietic damage by mustard gas and of the doubts concerning the existence of status lymphaticus—again to mention but a few. The inadequate treatment of chronic hemolytic jaundice and other conditions may, of course, be properly explained by the limitations of a single volume. In summary, then, we believe this to be a good text and are glad now to own a copy; but we also believe that the second edition will be superior to the first.

E. K.

DAS HÄMORRHOIDALLEIDEN, SEINE KOMPLIKATIONEN UND DEREN BEHANDLUNG. By DR. KASPER BLOND and DR. HERBERT HOFF, with a foreword by PROFESSOR DR. LEOPOLD SCHÖNBAUER. Pp. 121; 50 illustrations, many in colors. Wien: Franz Deuticke, 1936. Price: Paper, M. 12; Bound, M. 14.40.

FISSURE IN ANO, fistula in ano, and periproctitis, as well as hemorrhoids, are considered in this monograph. The discussion of these lesions is reasonably complete although not exhaustive. It includes historical material, pathology, diagnosis and treatment.

Two of the concepts in the book will be new to most readers. The authors believe that the hemorrhoidal diseases play an etiological rôle in diseases of the bile passages. They support this contention not only by anatomical considerations, but by a carefully controlled statistical study of the occurrence of hemorrhoidal diseases in patients coming to cholecystectomy.

The other unorthodox concept is that fistula in ano results from a purulent thrombophlebitis in the hemorrhoidal plexus. The authors present their personal observations on the development of fistulae in support of this theory.

The book is excellently illustrated with colored drawings, photographs, and Roentgen ray views of fistulous tracts following injection with opaque material. A number of references are cited in the text, but no systematic bibliography is afforded.

J. R.

AMEISENSÄURE ALS HEILMITTEL (Formic Acid as a Therapeutic Agent). By SAN-RAT DR. MED. ALBRECHT REUTER, Greiz. Pp. 14. München: Otto Gmelin, 1936. Price, M. 0.68.

A BRIEF summary of a book by the same author and publisher (1927), which must be consulted if one wishes to "experience joy in formic acid therapy." It is homeopathy of the 18th century, claiming cures of acute diseases ranging from acute rheumatic fever and gonorrheal salpingitis or epididymitis to puerperal septicemia, nephritis, and cystitis, and of chronic disorders such as arthritis deformans, tuberculosis of lungs, larynx, bones, and skin, Addison's disease, falling hair, cancer, asthma, gastric ulcer, and myopia—all by subcutaneous or intravenous injection of formic acid (it must come from the ant, and can be obtained from a specified pharmacist.) in dosage of the order of 0.3 to 0.5 cc. of dilutions ranging from 1 to 100,000 to 1 followed by 199 ciphers. It may surprise the reader—as it did the Reviewer—that a certain school of physicians still cling to such beliefs. C. S.

NEW BOOKS.

The Development of Modern Medicine. An Interpretation of the Social and Scientific Factors Involved. By RICHARD HARRISON SHRYOCK, Professor of History, Duke University. Pp. 442; illustrated. Philadelphia: University of Pennsylvania Press; London: Oxford University Press, 1936. Price, \$4.00.

The Cyclopedia of Medicine. Vol. 13, Revision Service. GEORGE MORRIS PIERSOL, B.S., M.D., Editor-in-Chief, EDWARD L. BORTZ, A.B., M.D., Assistant Editor. Chief Associate Editors: W. WAYNE BABCOCK, A.M., M.D., Surgery, CONRAD BERENS, M.D., Ophthalmology, P. BROOKE BLAND, M.D., Obstetrics and Gynecology, FRANCIS L. LEDERER, B.S., M.D., Otology, Laryngology and Rhinology, A. GRAEME MITCHELL, M.D., Pediatrics. Pp. 1063; 190 illustrations. Philadelphia: F. A. Davis Company, 1937. Price, \$12.00.

Clinical Implications of Modern Physiologic Hematology. (Beaumont Foundation Lectures.) By CHARLES A. DOAN, B.S., M.D., Professor of Medicine and Director of the Department of Medical and Surgical Research, College of Medicine, Ohio State University. Beaumont Lecturer for 1936. Pp. 160; 12 illustrations, 52 charts and 8 tables. St. Paul, Minn.: Bruce Publishing Company, 1936. (No price given.)

La Ponction de la Rate. By P. ÉMILE-WEIL, Médecin des Hôpitaux, P. ISCH-WALL, Assistant à l'Hôpital Tenon, Suzanne Perlès, Chef de Laboratoire à l'Hôpital Tenon. Pp. 148; 23 illustrations, some in colors. Paris: Masson & Cie, 1936. Price, 35 fr.

The True Physician. The Modern "Doctor of the Old School." By WINGATE M. JOHNSON, M.D. Pp. 157. New York: The Macmillan Company, 1936. Price, \$1.75.

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PROGRESS OF MEDICAL SCIENCE

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UNDER THE CHARGE OF

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THE RELATIONSHIP OF MENINGOCOCCUS CARRIERS TO THE INCIDENCE OF CEREBROSPINAL FEVER.

THE control of cerebrospinal fever is one of the unsolved problems of epidemiology. The disease continues to occur sporadically throughout the United States with characteristic seasonal increase in the late winter and spring. Here, there and yonder it suddenly becomes virulent, attains epidemic spread, prevails for a time, and disappears. In limited geographic areas there are alternating periods of unusual prevalence and relative rarity.

In spite of much work, little of fundamental value has been added to knowledge of the conditions which determine these distributions since the monograph of Netter and Debré,²² published in 1911, and the review by Frost,¹¹ in 1913. Experiences during and since the World War have, however, led to a better understanding of the biology of the meningococcus group of organisms and of the relationship between the distribution of carriers of meningococci and of cases of cerebrospinal fever.

Serological "Typing" of Meningococci. The accumulated experience of bacteriologists brought about a general recognition of the fact that although meningococci fall into a reasonably homogeneous group morphologically and culturally, they exhibit wide variation in their antigenic structure and in their pathogenic potentialities. Attempts to classify the multiplicity of strains by means of agglutination and agglutinin absorption led to the adoption in England and America of the Gordon-Murray Types I, II, III and IV, and in France of the Nicolle, Debains and Jouan Types A, B, C and D. Ability to classify strains serologically has led to exploration of the possibility that the antigenic composition thus identified might be correlated with those qualities which are grouped together under the term "virulence," and that this might hold the key to a better understanding of the irregular behavior of meningococci in the causation of disease and in the origin of epidemics.

In 1931, Branham, Taft and Carlin² completed an exhaustive study of the serologic classification into the 4 types of Gordon and Murray of 235 strains of meningococci isolated in various parts of the United States during the period 1928-1930; 215 were from spinal fluids, 5 from blood cultures and 15 from the rhinopharynx of carriers. This experience afforded information of value both on the side of the technical problems involved and the distribution of "types" in this country.

On the technical side, they^{1a} confirmed the experience of others with regard to the difficulties encountered in the serologic classification of this group of organisms. A minority of strains, about 20%, were agglutinated strongly by only a single type serum and could, therefore, be easily identified as to their Gordon grouping. This was particularly true of strains belonging to Type II or IV. Although there was some overlapping, they tended to be fairly distinct. On the other hand, with the remaining strains comprising about 80% of those studied, diversity of antigenic pattern was the rule rather than the exception. Nor was this pattern stable. Although a strain might be fairly "narrow" or type-specific immediately after isolation, with transfer on artificial media it tended to become antigenically "broader." All of the remaining strains were finally placed in either Type I or III, but the classification was not sharp nor entirely satisfactory. One type merged into the other, and some seemed to have antigen in common with II or IV. Thus, a majority of the strains of meningococci encountered could not be assigned to "narrow" types—as is possible for example with the pneumococci. They could be assigned only to the broad antigenic groupings.

Admitting the limitations of this method of classification, Branham and her co-workers compared the grouping of the strains of meningococci isolated between 1927-1930, with that obtained in a similar study by Butterfield and Neill⁴ of 128 strains isolated during the World War period, 1918-1919. They found that there had been a shift toward a greater predominance of strains in the I and III groupings, with a corresponding decrease in the number of strains assigned to Type II. *N. flavescens* n. Sp. (Branham, 1930) had been described in the meantime, and 5.9% of the strains recovered in the later period were identified as belonging to this species.

The shift in antigenic pattern of the prevailing types of meningococci as indicated by comparison with the Gordon type strains and sera was confirmed by the experience of the New York State Board of Health (Kirkbride and Cohen¹³). Between 1918 and 1930 a number of strains were typed each year, 431 in all. During the entire period not a single strain was identified as belonging to Type IV. The number of strains classified in Types I and III (or I to III) increased from about 35% in the earlier identification to 70% in the later, while those classified in Type II decreased from about 35% to less than 5%. Apparently, then, the prevailing *antigenic types of meningococci tend to change* with the passage of time.

Distribution of "Types." In studying the relationship of strain classification to geographic locality, admitting that the information is fragmentary, Branham *et al.*² noted that all Type IV strains received were from Chicago, except one, and that one came from Kansas City. Their study further showed that in the sharply localized outbreaks

in Salt Lake City, Utah, and Twin Falls County, Idaho, in 1928-1929 all of the strains examined, 10 in number, were practically identical (Type I). Two strains from a little outbreak in Rocky Mount, North Carolina, belonged to Type II. The first group of cultures from the Detroit epidemic of 1928-1929 behaved in identical manner, whereas those received later from the same epidemic varied widely within the I and III range. The San Francisco strains came from two different outbreaks, separated by 1 year; the first group received consisted of practically identical I's, and the second of equally similar III's. The strains received from Indiana were chiefly III's which might have been placed in several subgroups. Every possible intergradation between I and III occurred among a large number of strains from Tennessee. Those received from Chicago were the most heterogeneous of all, falling into all 4 groups, and *N. flavescens* as well. (See also Pope and White.²⁶)

In their study of the outbreak at Chatham Naval Hospital in England, Dudley and Brennan⁶ roughly classified 147 cultures isolated from cases and carriers between May and October, 1933, according to the Gordon types. Type II had 121, 13 were Type III, 12 were indistinguishable or inagglutinable, a solitary culture agglutinated with Type I serum only. There was no doubt that Type II predominated up to October, 1933, but in the following month with about half the cultures it was impossible to distinguish whether they belonged to Type II or III. In February and May of the following year, Type III predominated over Type II, 29 of the former to 11 of the latter, 4 II-III's, 4 I-II-III's and 2 IV's. After completion of this serologic investigation, the Standard Laboratory at Oxford, who supplied the specific type sera, issued a circular in which it was stated that Types II and IV meningococci belong to a "large heterogeneous group" of organisms having little or none of the characteristics of the original Gordon Types II and IV. Therefore, they proposed in the future to issue only 2 diagnostic sera, Group I, equivalent to Gordon's Types I and III, and Group II containing antibodies to several of the commoner antigens, not in Group I-III. In accordance with this classification of *N. meningitidis*, Group II was at first predominant at Chatham, but was later replaced largely by Group I—the carrier rate remaining constant throughout the substitution at the phenomenal level of 50%.

Without quoting further observations, it appears that *small isolated outbreaks may be due to a single serologic type of meningococcus, but that in more extensive epidemics all varieties may appear and that in the same epidemic the predominating antigenic type may change.*

Virulence of "Types." The opinion expressed by Rake,²⁷ that Types I and III and related strains are rare in the general population during endemic times and are probably responsible for most epidemics, while Type II is more saprophytic in nature, occasionally giving rise to endemic cases, is open to question as a generalization applying over a long period of time and wide geographic area. The evidence at present available, on the contrary, indicates that strains in all 4 Gordon types may at times become highly pathogenic, and give rise to cases and outbreaks.

The term "virulence" is a vague one, but for purpose of discussion, it may be said to involve two qualities, that is, "toxicity" and

"invasiveness." The former attribute can be roughly measured by intrapleural, intravenous, intracisternal, subdural or intraperitoneal injections of heavy suspensions of meningococci, living or dead, into laboratory animals—mice, guinea pigs, rabbits. It has been found to be a labile character, usually present in strains freshly isolated from spinal fluids, largely dependent upon conditions of growth for its maintenance (Murray and Ayrton²¹), easily lost, and restored with difficulty, if at all, by animal passage.

The relationship between toxin production and virulence is by no means a closed chapter. Ferry and his co-workers⁷⁻¹⁰ claim that bouillon filtrates of young freshly isolated cultures contain soluble or extracellular toxin, specific for each of the 4 Gordon types as well as a toxin common to all types. Malcolm and White,¹⁸ and Maegraith,¹⁷ on the other hand, maintain the earlier conception that the meningococcus is a fragile cell, subject to rapid autolysis, and that the action of Ferry's "exotoxin" is referable to an endotoxin or its cleavage products.

Up to recently, it has not been possible to investigate "invasiveness" satisfactorily in animals. An infection somewhat similar to that in man can be produced in Rhesus monkeys, as originally shown by Flexner, by lumbar subdural injection of large quantities of meningococcus culture, but the species are relatively refractory, the results irregular, and the disease, when produced, a highly fatal acute toxemia like the fulminating human case.⁷ The method proposed by Miller¹⁹ appears to be an advance. By adding boiled mucin to suspensions of meningococci, injected intraperitoneally into mice, the ability of the organism to survive, multiply and bring about death of this animal can be measured more delicately than has previously been found possible. This technique has become known as the "mouse-mucin" test. Silverthorne and Fraser^{20a} have discovered that strains of meningococci vary in their ability to thrive in a sample of human blood having no bactericidal power, and that this quality is, in general, parallel to the virulence of strains as judged by the mouse-mucin test. It seems probable, though it is by no means established, that such tests may be used as a rough measure of the "invasiveness" of strains for the human host.

It suffices to summarize here that on the basis of present knowledge *type does not per se determine virulence*. The correlation of antigenic pattern with "virulence" has not yet been established. *Just as strains of any type (I, II, III or IV) may become rough or smooth, they may become relatively virulent or avirulent within broad limits, and probably do so under natural conditions.*

Carriers During Non-epidemic Periods. On the basis of the observations made during the World War, it is conservatively estimated that in non-epidemic times meningococci will be found to be present in the rhinopharynx of 2 to 8% of healthy civilians; the actual proportion will depend to a certain extent on the time of the year.³⁰ Two recent studies are of interest in this connection.

Rake^{27a} made repeated examinations of individuals working on one floor of one of the building units of the Rockefeller Institute in New York City, 1932-1934. During 20 months, 24 persons were subjected to rhinopharyngeal swabbings which were carried out approximately

weekly. Ten individuals carried meningococci at some time or other during the period, 5 were constant or chronic carriers, 2 intermittent, and 3 transient. Four of the 5 chronic carriers harbored the organism from 21 to 26 months and were still positive when last observed. Rake emphasizes that 3 negative swabs obtained at weekly intervals do not prove the absence of meningococci from the rhinopharynx. As with other carrier conditions a series of negative cultures may be followed by a positive.

In another study Rake investigated 569 young men between 18 and 25 years of age, picked from all sections of the community for the Civilian Conservation Corps while in concentration at Fort Slocum during the spring. Eighty-three were swabbed on 3 successive weeks, 291 on 2 successive weeks and 195 only once. Twelve carriers were found (2.1 %).

Silverthorne,²⁸ working in Toronto, Canada, in a preliminary study isolated meningococci from 16 out of 125 medical students examined. Subsequently, during a 2-year period he made observations on 63 healthy adults, mainly physicians and technicians, at approximately monthly intervals. The monthly percentage of individuals positive for meningococci varied between 16 and 28 (average, 20). For the 2-year period, of 63 adults tested, no less than 26 (41 %) showed the presence of the meningococcus in the rhinopharynx at one time or another, 11 fairly persistently. There were no cases of cerebrospinal fever among this group.

It appears from these studies that *the proportion of healthy persons harboring meningococci during non-epidemic periods is quite variable, and may at times reach a high figure without the occurrence of cases.*

Carriers During Epidemic Periods. The observations of Bruns and Hohn³ and of Glover^{12,20} have been widely quoted as indicating that the proportion of carriers in a community is roughly proportional to the course of the epidemic. Glover has placed the danger line at 20 %. Dudley and Brennan⁶ question the accuracy of any such generalization. Chatham Naval Hospital, between January, 1932, and March, 1933, had 11 cases of cerebrospinal meningitis. Among 211 contacts of these cases, 27 carriers were found as a result of the examination of a single nasopharyngeal swab from each, a carrier rate of 13 %. During a subsequent period, March, 1933, to May, 1934, with the same technique, 260 out of 481 of the persons in the same station were found to be positive (54 %), yet during this period there was not a single case of meningitis among the 10,000 sailors, soldiers and airmen garrisoned in the Chatham area. By way of contrast, about the same time 6 cases of meningitis were admitted to the Portsmouth Naval Hospital, but only 9 meningococcus carriers were found among 177 contacts of these cases (5.1 %).

In the Detroit outbreak, 1928-1931, Norton and Baisley,²⁴ between February and June, 1929, found 539 out of 2115 (25 %) of the contacts to be positive. Thereafter, although cases continued to occur in large numbers, the percentage of positive contacts dropped to about 3.4 % and remained rather uniformly at that figure for 1½ years. During the same period, repeated examinations made on small groups of persons who were not in contact with cases, 1991 in all, showed about 1 % to be positive.

Kuhns¹⁴ observed an epidemic in Atchinson County, Missouri, in the spring of 1935. Of 17 cases in the area, 9 were among the personnel of a C.C.C. Camp. Cultures were made on all enrollees in the camp at weekly intervals for 4 successive weeks. The population varied from 250 men to 213. The greatest number of enrollees to yield positive cultures from the rhinopharynx at one time was 11 (4.4%). In another C.C.C. Camp 20 miles distant, where there were 196 men and no cases of meningitis, cultures similarly made showed 7 (3.5%) to be positive. All of the "positive" cultures were confirmed by agglutination, but no details are given regarding the serum or sera used for this identification.

Laybourn,¹⁵ on the basis of his investigation of several small institutional outbreaks, noted the lack of correlation between carrier rate and case rate and believed it to be explained very largely by inclusion in the carrier rate of persons harboring "saprophytic" meningococci. He emphasized the importance of "effective" carriers who harbor what he terms "epidemic strains" over a long period of time and intermittently distribute them. He identifies "epidemic strains" with the antigenic pattern designated as Gordon Type I-III on the basis of Rake's^{27b} opinion, and insists on the importance of "typings" in all carrier surveys.

It is evident from these studies that *the relationship of the carrier rate to the case rate is not constant. There are too many variables in each situation.*

Variable Factors in the Carrier-Case Ratio. These may be classified into technical and biologic. As regards the first it is perfectly obvious that the methods used will directly influence the numerical result obtained. This applies particularly to the bacteriologic technique employed,^{1b,6} and to the number of examinations made upon each individual.^{24,27a} A "rate" is ordinarily based upon a single examination of each individual; it is obviously an index, and by no means reveals all who are harboring meningococci.

On the biologic side, it is equally obvious that the ratio will depend upon the "virulence" of the prevailing strains of meningococci with reference to the "resistance" of the population group exposed.

It is well recognized that strains recovered from the nasopharynx of healthy individuals vary widely in their pathogenic potentialities. It is conceivable that certain strains may become well adapted to growth on the respiratory mucous membrane, show an unusual ability to spread from individual to individual, *i. e.*, be highly "infectious," yet have relatively low powers of "invasion," and *vice versa*. As has been pointed out, it has not been established by the evidence available, that such qualities are directly correlated with Gordon type. The serologic "typing" of meningococci does not serve to distinguish "virulent" or "epidemic" from "saprophytic" or "non-epidemic" strains. It gives information as to the similarity or dissimilarity of antigenic composition of strains recovered from carriers as compared with strains isolated from cases. If the "epidemic significance" of carrier strains is to be determined, a test for "virulence" would seem to be more appropriate on the basis of present knowledge than is "type" classification.

Mass Immunity and Individual Resistance. That there is a high degree of resistance to the meningococcus is evident from its selective

attack in an exposed community and the low secondary attack rate in family groups. In the Detroit epidemic, Norton²³ found that only 46 out of 6416 contacts exposed to a case in the same house came down with the disease, *i. e.*, the secondary attack rate was 0.7%.

If a carrier rate of 20% prevailed and the average duration of the carrier state is 2 weeks, practically every person in a community would have harbored the organism in their rhinopharynx at least once in 3 months. When the meningococcus is prevalent, it is apparent that a very high proportion of the persons in the community may be exposed sooner or later. This is particularly true of military or naval units, institutions, etc., where a large number of persons are brought into close contact. Yet usually less than 1 in 100 come down with cerebrospinal fever.

That this resistance is to some degree acquired is suggested (a) by the decreasing attack rate with advancing age (for example, see Norton and Gordon²⁵), and (b) the greater susceptibility of recruits. In the latter connection, a recent study by Cook of the "Incidence of Cerebrospinal Fever in the United States Navy as Related to Length of Service and Season of Enlistment" is of particular interest. He found, in brief, that the attack rate in men with less than 3 months' service was 10 to 46 times as great as that of men with more than 1 year of service, that in 1926-1929 the attack rate per 100,000 in men of more than 2 months' service was 21.4 at training stations, and 2.4 elsewhere, and that during the same period men who enlisted in the months of October to February experienced an attack rate during their first year of service of 35.5 per 100,000 as compared with a rate of 16.3 for those who enlisted from March to September. In other words, if a recruit were "seasoned" in small commands during the period of the year when the incidence of cerebrospinal fever is lowest, his chances of escaping an attack were greatly increased over those of recruits who entered the large training stations during the fall and winter. This observation together with other data on the selective distribution of cases of cerebrospinal fever and of the frequency of the meningococcus carrier state suggests that subclinical immunization from postnasal infection may play an important rôle in the development of immunity.

The mechanism of this immunity is unknown, but the recent observations of Silverthorne and Fraser^{29a} are of interest. In 1934, they demonstrated that samples of blood from many adults were bactericidal to a recently isolated strain of meningococcus. Other adults and infants failed to manifest this property in their blood. Two infants with meningitis possessed little or no bactericidal power at the onset of their disease but developed it after recovery. In 1935,^{29b} the same authors found that the bactericidal principle was present in serum or plasma, that it depended upon the presence of complement for its action, and that it was highly specific for the meningococcus. In 1936,²⁵ using as a control test a previously known non-bactericidal sample of blood, and a virulent recently isolated cerebrospinal fluid strain of meningococcus, they demonstrated that samples of blood from 5 carriers were bactericidal to this virulent strain and to each of the 5 carrier strains.

Ferry and his co-workers⁷⁻¹⁶ and Kulus¹⁴ have shown that certain individuals show a reaction to an intradermal injection of diluted

meningococcus filtrates. They interpret such reactions as an indication of "susceptibility" to meningococcus toxin similar to that indicated by a positive Dick or Schick test. They fail to establish what relation, if any, this *skin "susceptibility"* to meningococcus toxin has to the susceptibility of the individual to an attack of cerebrospinal fever. Until such a relationship is proved, the test cannot be accepted as indicating the presence or absence of immunity.

Administrative Control. After reviewing the observations made in recent years, one is inclined to agree with McCoy¹⁶ and with Dudley and Brennan⁶ that the attempt to control the occurrence of cerebrospinal fever by detection, segregation and treatment of meningococcus carriers is, under the usual conditions of either military or civil life, an impractical, inefficient and relatively unproductive procedure. The meningococcus is simply one of the many potentially pathogenic micro-organisms that must eventually make their way from the nasopharynx of one human being to another. A vast majority of individuals either have, or develop, sufficient immunity to resist its invasion of the blood stream and meninges. As with other diseases in the respiratory group, it would seem that the effort must be directed, not to prevention of the spread of the organism, but to measures which will reduce the risk of clinical attack. In naval and military commands, on the basis of Cook's studies, affording the recruit a maximum opportunity to develop natural immunity under favorable conditions of exposure, promises reduction in the incidence of the disease. In the final analysis, control must wait upon the development of a dependable test for immunity and a satisfactory immunizing agent. It is only the occasional individual who needs the artificial antigenic stimulus.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA,

SESSION OF JANUARY 18, 1937.

The Use of Rats in the Study of Anticonvulsant Drugs. WILLIAM L. SAMPSON and L. FERNANDEZ (Merck Institute of Therapeutic Research), Rahway, N. J. Intraperitoneal injections of a 2% emulsion of oil of thujone will produce epileptiform convulsions in the rat identical in character with those produced in the rabbit. The quantity of oil of thujone necessary to elicit a distinct convulsive response is well below the *L.D.O.* of the drug. Repeated administration of the drug in no way influences the growth rate of the animal. The sensitivity of different rats and the day to day response of any individual animal is subject to marked variation. However, if sufficiently large groups of rats (20 or more) are used the results are remarkably consistent. Strychnine increases and luminal decreases the sensitivity of rats to thujone convulsions. The responses of groups of rats to camphor or picrotoxin convulsions, while somewhat different in character, are equally consistent as the response to oil of thujone. Since experimental convulsions can be satisfactorily produced in rats, this animal may well be the animal of choice in the study of anticonvulsant drugs because large groups of a uniform strain can be handled with a maximum of economy in time, space, and cost of maintenance.

Spectrophotometric Studies of the Color Development in the Analysis of Sugar by the Benedict Method and of Cholesterol by the Liebermann-Burchard Reaction. F. WILLIAM SUNDERMAN and J. RAZEK (Laboratory of Research Medicine, University of Pennsylvania). The development of color in sugar solutions by the Benedict method and in cholesterol solutions utilizing the Liebermann-Burchard reaction was studied by means of a photo-electric spectrophotometer which recorded within 10 seconds the transmission at each wave length throughout the visible range. The first curve was obtained 2 minutes after preparation of a given solution and subsequent curves at intervals up to 1 hour. These studies afford a basis for selecting the optimal spectral zone for colorimetry in these two methods.

Cholesterol in Human Liver Bile. CECILIA RIEGEL, I. S. RAYDIN and H. J. ROSE (Harrison Department of Surgical Research, University of Pennsylvania). Daily specimens of hepatic bile collected by external drainage from a large number of patients were analyzed for cholesterol concentration. It was found that:

1. There was no correlation between fluid intake and cholesterol concentration.

2. There was no correlation between amount of bile drained externally and cholesterol concentration. In 2 patients no relationship was observed between total 24-hour volume of bile and cholesterol concentration.

3. When cholesterol concentration was low, bile salt concentration was also low, and *vice versa*.

4. Patients having badly damaged livers had low cholesterol concentrations in the hepatic bile. Those with only slightly damaged livers had high cholesterol concentration in hepatic bile.

The Physical Properties of the Mammalian (Rabbit) Oöcyte and its Protecting Membranes. G. S. DE RENYI and D. P. MURPHY (Department of Anatomy, University of Pennsylvania, and Gyneccean Hospital Institute). Rabbits were made to ovulate by intravenous injection of pregnancy urine (Friedman's method). They were killed about 12 hours after the injection and the oöcytes, which are at that time in the upper part of the oviduct, were washed out with warm saline. Fertilization in the rabbit occurs in the upper part of the oviduct shortly after ovulation. Therefore, our material was suitable for ascertaining the physical properties of the oöcyte and of its protecting membranes at a stage when it is prepared to receive the spermium.

As is generally known, oöcytes in this stage are in possession of two protecting membranes. However, the physical properties of these sheaths have not yet been systematically studied.

The microdissecting method reveals a cement substance between the cells of the outer, cellular membrane, *i. e.*, the cumulus oöphorus. This intercellular substance has a higher refracting index than the substance of the cells. It can be pulled out into long threads which finally break under extreme tension. The ends then retract. There is no doubt that the intercellular substance of the cumulus is extremely viscid and elastic.

The zona pellucida when torn with needles breaks, leaving a sharp serrated edge. It expands to a certain extent when the cavity of the zona pellucida is injected with saline under high pressure. Released from pressure, the zona fails to regain its original form and size. It is an inelastic, rigid membrane. Microinjecting experiments seem to prove that both membranes are continuous. There is no evidence of a preformed channel through which the injected fluid might escape.

The primary oöcyte is covered with a highly refractile membrane, *i. e.*, the oölemma. When injured, it does not disintegrate like the surface membrane of many invertebrate ova.

The substance of the oöcyte is viscous and plastic. Its granules do not perform Brownian motion. It disintegrates slowly when exposed to isotonic saline.

Observations on Thyroid Tissue Implanted in a Transparent Chamber Installed in the Rabbit's Ear. ROY G. WILLIAMS (Laboratory of Anatomy, University of Pennsylvania). Autogenous grafts of thyroid gland were implanted in a transparent chamber installed in a rabbit's ear. Four grafts were used which varied in diameter from 0.1 to 0.3 mm. and were about 0.1 mm. thick. One graft survived but did not grow. Vascularization began within 24 hours and was complete by 4½ days. With the compound microscope the follicles could be seen distinctly in optical section and changes recorded by camera lucida tracings. The nuclei of the thyroid cells were only occasionally visible in some follicles. The colloid appeared structureless except for a few small indistinct granular masses and one or more large vacuoles. Two types

of follicles were observed: one which was small with a relatively thick wall and containing one or two vacuoles, another which was larger, with thinner walls and a larger number of vacuoles. These vacuoles were not arranged next the cells and were, apparently, not the same structures as the vacuoles seen in fixed sections.

The implant was observed daily for 30 days. Three injections of a stock preparation of "*antuitrin*" were then given subcutaneously on successive days—1 cc. the first day, 2 cc. the second, 5.5 cc. on the third. These produced a swelling of the entire follicle, walls and colloid, followed by a sudden but small drop with the last dose. Three days after the last dose there was some increase in thickness of the follicular wall and decrease in colloid. This was followed by a shrinkage of wall area and an increase in area of colloid. Six days after the last of the previous injections, 3 doses of "*thyroprotein*," 2 cc. each, were given subcutaneously on successive days. These injections produced a further diminution in follicular wall area and an increase in colloid. These experiments were solely for the purpose of determining whether or not the graft follicles were capable of responding. Six days after the last injection the graft was fixed together with a sample of thyroid tissue from the neck of the same animal. The sections of the graft were similar to those from the control and were regarded as being normal and healthy in appearance.

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ORIGINAL ARTICLES.

STUDIES OF BLOOD FORMATION IN THE FETUS AND
NEWBORN.

III. THE RELATION OF ANTI-ANEMIC PRINCIPLE. ASSAY OF FETAL
LIVER AND PLACENTAL EXTRACTS IN CASES OF PERNICIOUS
ANEMIA AND IN MOSQUITO LARVAE.*

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IN earlier papers,^{29a,b} in which the number, size and other morphologic characteristics of the red corpuscles of the fetus were described, it was pointed out that the changes which occur in the blood of the fetus as it develops, are very similar to those which are found in cases of pernicious anemia during the period of response to an effective, continuous and extremely potent stimulus to blood formation. Because of this similarity, it was suggested that the anti-anemic principle of Castle, which causes the increase in number and the decrease in the size of the red corpuscles in pernicious anemia, may be the same or very similar to the substance which

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causes the blood of the fetus to develop in the manner described. Since this principle is thought to be formed by the interaction of a factor in the diet and a secretion from the stomach,⁴ it seemed plausible that it should be lacking in the fetus except insofar as it might be supplied by the mother. The utilization by the fetus of anti-anemic principle derived from the mother would explain the development of pernicious anemia of pregnancy, and deficiency of this substance in the fetus might explain some of the anemias of newborn and premature infants.

The purpose of this communication is to report the results of investigations seeking to determine the relationship between fetal hematopoiesis and that observed in cases of pernicious anemia treated with liver.

Gastric Function in the Fetus and Newborn. While the functional state of the stomach in the fetus and newborn, in view of Castle's hypothesis,⁴ is a matter of considerable interest, it is a subject which has not been completely explored. Nor is it one which lends itself readily to investigation.

Kirk¹⁶ studying in Bensley's laboratory the histogenesis of the gastric glands of the pig, found that the gastric epithelium, derived from the endoderm, remains as a single layer of cells. The embryonic gland cells which can be seen at the 2 cm. stage (10 days) constantly differentiate. Some of these become parietal cells. By the 6 cm. stage (44 days) mucus cells are found. At the 19 to 20 cm. stage (84 to 88 days) zymogenic and serous chief cells appear. In the pig at 7 cm. (about 49 days) certain definite gastric regions become differentiated. Cytodifferentiation is practically complete in the pylorus at 9 cm. (54 days) although the size of the cells, the depth of the goblets and other details alter somewhat after this. According to Kirk, the fundus is moderately well differentiated by the 19 cm. stage (85 days), but in the cardia cytodifferentiation is not complete even at birth (114 days).

The development of the gastric mucosa in other mammals and in the human embryo is apparently similar to that in the pig, although, it seems, the details have not been as thoroughly studied as in this animal. In the human embryo²⁰ at 42 mm. (about 71 days), elaboration of mucus may be observed. In the 120 mm. embryo (114 days), parietal cells and zymogenic cells can be distinguished. The pyloric and cardiac portions of the stomach become differentiated between the fifth and sixth months¹⁵ but even at birth the full number of glands is not present.

The gastric ferments in the embryo and newborn received early attention. In 1874, Zweifel³¹ reported that pepsin is present in the gastric mucosa of the newborn, and also found this ferment in the stomach of a premature infant. Grützner's preliminary investigations¹⁰ indicated that the stomach of embryos of the sheep, cow, pig and dog contains small traces of pepsin but no acid. He found

that the pepsin content increases as the fetus develops. Moriggia²¹ found an acid reaction and evidence of digestive activity in the "labmagen" of the cow embryo as early as the third month. Hammarsten¹¹ could demonstrate no peptically active substances in the stomach of dogs during the first 2 weeks of life but the gastric secretion at birth contained sufficient acid to coagulate milk. His findings in newborn kittens and rabbits were similar to those in dogs. Wolffhügel³⁰ who confirmed these results, was uncertain whether the acid present was lactic acid or free hydrochloric acid. Gmelin⁷ claimed that there is only lactic acid in the stomach of pups at birth, but Cohnheim and Soetbeer⁵ in sham feeding experiments found free hydrochloric acid as early as the first day. Langendorff¹⁸ found trypsin even though pepsin was absent in newborn dogs and cats. In the rabbit, however, even in young embryos, Langendorff demonstrated both of these enzymes and van Puteren²² found that acid appears in the stomach of rabbit embryos in the last third of the developmental period.

Langendorff¹⁸ studied several hundred embryos of the pig and found traces of pepsin in the gastric mucosa as early as the 120 to 135 mm. stage (63 to 67 days), as well as larger amounts in later stages (170 to 190 mm., 77 to 85 days). The amount during intra-uterine life was never great, however, and showed individual variations. He described the contents of the stomach as tenacious mucoid material, devoid of acid and lacking pepsin even when the enzyme could be demonstrated in the mucosa. Langendorff found pepsin also in the gastric mucosa of fetuses of the cow and the rat.

In the human fetus, according to Langendorff¹⁸ pepsin appears at the end of the third or the beginning of the fourth month and after this it is quite plentiful. In two fetuses of 150 and 170 days, respectively, the writer found 1.5 cc. of watery fluid in the stomach which gave a yellow reaction with di-methyl-amino-azobenzol. In the stomach of the older fetus, there were 12.5 units of combined acid. From the stomachs of several other fetuses no fluid was obtained. Extensive studies¹² of the gastric secretion of newborn infants before they were given food were reported by Hess, who found considerable amounts of hydrochloric acid. Rennin, pepsin, and lipase were also obtained.

In pups and kittens Sutherland²⁵ found no spontaneous secretion of gastric juice *in utero*, but did find some secretory response to gastrin when the fetuses were within a few days of term. The secretory response to gastrin increased with age, at least for the first few days. In guinea pigs, Sutherland discovered that there may be a spontaneous secretion of acid gastric juice during late intrauterine life. In newborn rabbits the gastric juice contained hydrochloric acid on the second day after birth.

Gastric motility appears early in fetal development. Tani²⁶ found that spontaneous movements occur in the stomach of the rab-

bit fetus when the body weight has reached 7.5 gm. and Kosh-toyantz and Mitropolitanskaya¹⁷ claimed that automaticity in the fetal human gastro-intestinal tract develops after the seventh week. Recently Friedman⁶ reported that spontaneous contractions of the stomach of the cat fetus are already present in fetuses of 58 mm. body length (about 36 days). In older fetuses the customary reactions to drugs such as pilocarpine and atropine occurred.

Heuser's¹³ observations in the opossum indicate that the fetal stomach in this species is capable of physiologic activity before its cytologic development is complete. The fetuses appear in the pouch as early as 10 days after the beginning of segmentation. Five days before birth the digestive tract of the opossum is no further advanced than it is in the 3-day chick embryo. At birth, the gastric glands are not developed and the epithelial cells are yet of a simple type. Nevertheless milk is digested.

It is thus evident that physiological activity may be possible in the stomach before birth. Whether this actually occurs is unknown and what bearing this would have on hematopoiesis in the fetus is likewise unanswerable. There is no information concerning the elaboration of "intrinsic factor" in the fetus nor do we know whether there is a source of "extrinsic factor." The content of amniotic fluid in this respect is unknown. It must be admitted that the formation of anti-anemic principle by the fetus itself is a possibility which cannot at the present time be dismissed. In the light of our present knowledge, it would seem more probable, however, that if the fetus requires anti-anemic principle, it derives this substance from the mother. In any event, precursor substances would ultimately be drawn from her.

Direct evidence bearing on these questions is difficult to obtain, but indirectly the following experiments may be of some significance.

The Effect on the Blood of the Fetus of the Administration of Liver Extract to the Mother and to the Fetus. Rabbits were mated in the laboratory and liver extract (Lilly 343, N.N.R.) was given intramuscularly, 5 cc. twice weekly. All of the animals appeared to be in good health and were given the same food. Three rabbits received liver extract, whereas 4 were used as controls. No appreciable change was observed in the red cell count, hemoglobin, mean corpuscular volume or reticulocytes of any of the pregnant animals.

Fetuses of equal age were removed from rabbits given liver extract and from control animals. Study of their blood suggested that no effect on the fetal blood is produced by the administration of liver extract to the mother. Thus the red cell counts of two fetuses of 21 days taken from a rabbit given liver extract, were 2,770,000 and 2,860,000 respectively, with mean corpuscular volumes of 108 and 109 cubic microns. The red cell counts of two fetuses of this age taken from a control rabbit were 3,400,000 and 3,240,000 respectively with mean corpuscular volumes of 112 and 115 cubic microns. These differences are no greater than those we have observed in fetuses from different mothers.^{23,6}

An attempt was also made to inject liver extract directly into the placenta. This was done by laparotomy, liver extract being injected into each placenta in one horn of the rabbit uterus, while no injections were made in the other horn. As might be expected, usually the fetuses died or were aborted. In one instance, however, 0.15 cc. liver extract (Lilly 343, N.N.R.) was injected on the tenth day of pregnancy into each placenta in the left horn of the uterus and the fetuses remained viable. Thirteen days later, hysterectomy was performed. The average red cell count of the fetuses in the right horn was 2,140,000 and the mean corpuscular volume was 150 cubic microns, whereas in the fetuses from the left horn an average erythrocyte count of 2,320,000 and mean corpuscular volume of 154 cubic microns were found. These differences were regarded as too small to be significant.

These experiments were not continued, not only because of their difficulty, but also because it was felt that a failure to influence the blood of the fetus by the administration of liver extract could not be interpreted as contradicting the hypothesis proposed. If it is assumed that the fetus already receives a maximal quantity of anti-anemic principle, then any additional amount cannot be expected to produce a demonstrable effect.

Anti-anemic Potency of Fetal Liver. In the adult mammal, particularly in swine, cattle and man, anti-anemic principle is found in the liver, where it is probably stored. This substance is not found in the liver of cases of pernicious anemia in relapse¹⁴ and following total gastrectomy in the pig the anti-anemic potency of the liver becomes progressively depleted.^{1,9} In a consideration of the rôle of Castle's principle in fetal hematopoiesis, information concerning the anti-anemic potency of fetal liver is thus of fundamental importance.

Berglund and his associates² fed powdered fetal calf liver, 300 gm. daily, to one patient with pernicious anemia. No reticulocyte response followed but the erythrocyte count rose. The latter change, however, might possibly have been the effect of an extract of adult liver given during the preceding 9 days which had been associated with a very slight reticulocyte response. Bence¹ stated that an extract made of the fetal liver of beef was as potent as extract made from adult liver and used this as evidence favoring his opinion that an interaction between two factors is unnecessary for the formation of anti-anemic principle. He seems, however, to have tested the fetal extract in one case only. Following injection of this extract, the reticulocytes rose irregularly to a maximum of 19% and the erythrocyte count, which was as low as 1 million, did not change. This cannot be considered to be incontrovertible evidence of the presence of anti-anemic principle in fetal liver and at best indicates that the quantity present is less in fetal than in adult liver. He also reported that an extract made from the liver of a suckling calf, given to a patient with less than 1 million erythrocytes, was associated with an increase in reticulocytes to 46% and a distinct rise in red cells and hemoglobin.

More convincing as regards the presence of anti-anemic principle in fetal liver is the report of Goldhamer *et al.*⁸ who made an extract of the liver of a 7-month human fetus. Twenty cc. of this extract, representing 65 gm. of fresh liver, produced an increase in reticulocytes to 17.6% in a patient whose erythrocyte count was 950,000 per c.mm. This was, however, quite clearly a submaximal response.

Method. For our own observations, the pig was chosen as the source of fetal liver. This was done not only because pig fetal liver was obtainable in adequate amounts but also because it has been demonstrated that, as regards the formation of anti-anemic principle, this animal may be compared with man. Desiccated hog's stomach is potent in the treatment of pernicious anemia²¹ and commercial liver extract (Lilly, 343 N.N.R.) is made from pork livers. Furthermore, as already pointed out, it has been shown that the anti-anemic potency of adult pig liver becomes greatly reduced following total gastrectomy.^{1,9}

The fetal liver was prepared as an extract for parenteral injection because, even though this entails a loss of 20 or 25% of the original potency of whole liver, the effectiveness of active material given by injection is very much greater than that given by mouth. The extracts were made in the Research Laboratories of Eli Lilly and Company by a modification of the method by which commercial extract derived from adult liver is prepared. The livers of fetuses of the second third of the gestation period (45 to 165 mm.) were used in the preparation of extract T 670; those of the third third (166 to 250 mm.) formed extract T 671; those of the fifth sixth are represented by extract T 702; and those of the sixth sixth, by T 703. Like the commercial product (Lilly, N.N.R.), these extracts were prepared in concentration such that 1 cc. represented 5 gm. of original fresh liver tissue.

Bence¹ pointed out that extract made from the livers of gastrectomized hogs is light opalescent in color rather than brown as is that made from normal liver. It is interesting to note that all of the fetal liver extracts were lighter in color and lower in the content of solids than extract made from adult liver. Whereas the latter is very dark and not transparent, with a content of 19 to 21 gm. % solids, extract T 670 was watery in appearance except for a dull yellowish color (solids 4.63%); T 702 was similar in appearance but slightly darker (solids 5.05%); T 671 was still darker (solids 7.63%); while T 703 was moderately dark and more nearly resembled 343 although it was quite transparent (solids 8.10%).

The extracts were assayed by giving uniform doses daily for periods of 6 to 15 days to cases of pernicious anemia during the stage of relapse. They were usually administered intramuscularly but in one instance extract was injected intravenously. Following the trial periods with fetal liver extracts, uniform daily doses of commercial Solution Liver Extract, Lilly N.N.R. were given. No other anti-anemic therapy was used. Reticulocyte counts were made daily and erythrocyte counts, hemoglobin and volume of packed red cells were determined at 5-day intervals.

Results. The results of this assay are summarized in Table 1. In Patient E. M., extracts T 670 and T 671 were ineffective in doses of 1 cc. for 10 days each, whereas extract made from adult liver caused a definite, though submaximal³ response. In Patient O. M., studies were less satisfactory because assay of fetal liver extracts could only be commenced after a response had already been obtained to adult liver extract. This patient's condition on admission was so serious that 20 cc. of Solution 343 (Lilly N.N.R.) was given. Administration of fetal liver extracts was commenced 21 days afterwards, at a time when the reticulocytes had again reached a low level and the erythrocyte counts had ceased to rise. In this

patient, as in E. M., doses of 1 cc. for 10 days of extracts T 670 and T 671 proved ineffective and the patient's condition became less satisfactory. It must be observed, however, that a clear cut response to Extract 343 in these doses did not immediately follow and an increase in the erythrocyte count occurred only after continued treatment with extract of adult liver.

In Patient T. E., T 670 again proved ineffective in these doses, as did T 702 and T 703. Adult liver extract was followed by a satisfactory response. Exact comparison of the potency of adult and fetal extracts cannot be made in this case, however, because the patient's condition by this time necessitated the administration of doses of adult liver extract which were considerably larger than those of the fetal extracts.

In G. A. C., T 670 in doses of 3 cc. had no effect whereas 343 in this dosage was followed by a maximal response. Extract T 702 was given to Patient B. D. in 10 doses of 3 cc. each. There was no reticulocyte response, nor did the hemoglobin or volume of packed red cells change although the erythrocyte count rose. Administration of extract 343 was followed by a maximal reticulocyte response.

Patient L. E., received extract T 703 in 6 doses of 10 cc. each. During this period the successive daily reticulocyte counts were 0.5, 0.9, 1.2, 0.7, — , and 0.7%. On the sixth day after administration of this extract had been commenced, the reticulocytes were 1.5%. Further observation without other treatment would have been desirable but this was not possible and administration of an extract (J. H. H.) prepared at this hospital from adult liver was commenced on this day. The reticulocyte counts on the succeeding days were 1.2, 1.3, 1.8, 5.4, 7.2, 7.2, 8.9, 8.9 2.1, 0.7, and 1.3%. Whether there may have been a very slight, delayed response to T 703 cannot be decided, but at least it was insignificant when compared with the effect of the extract made from adult liver.

The ineffectiveness of extract T 703 was further demonstrated in Patient I. G., who received 9 doses of 3 cc. each and 3 doses of 10 cc. each. Administration of this extract was commenced 5 days following a single dose of 3 cc. adult liver extract which had no apparent effect and could not be considered to have prevented the appearance of a response to T 703. Following the administration to the patient of another extract of unknown potency, the injection of adult liver extract in doses of 1 cc. daily was followed by a well marked reticulocyte response.

As a final test of extract T 703, it was administered *intravenously* to Patient E. N., in 10 doses of 10 cc. each. This was entirely without effect (Table 1 and Figure 1).

Assay of these fetal liver extracts indicated quite clearly, then, that they were of no value in the treatment of pernicious anemia. The extract derived from the livers of pigs in the second third of the gestation period (T 670) was ineffective when given intramuscularly in 10 doses of 3 cc. (Patient G. A. C.), as well as in smaller doses (Patients E. M., O. M., T. E.), although extract made from adult liver caused a maximal response when given in 3 cc. doses (Patient G. A. C.). Administration of extract made from the livers of pig fetuses in the last third of the gestation period (T 671) which was administered only in 1 cc. doses (Patients E. M. and O. M.) was associated with a very irregular, probably non-specific, reticulocyte variation in 1 patient and with no change in reticulocytes in another.

The anti-anemic potency of the livers of fetuses of the last third of the gestation period was tested further by using extracts made

TABLE 1.—SUMMARY OF RESULTS OF ASSAY OF FETAL LIVER AND PLACENTAL EXTRACTS IN CASES OF PERNICIOUS ANEMIA.

Patient.	Period one.					Period two.					Period three.					Period four.											
	Extract.		Blood.		Retics.	Extract.		Blood.		Retics.	Extract.		Blood.		Retics.	Extract.		Blood.		Retics.							
	No.	Dose cc. x days.	At end Initial.	Ini- tial.	High- est.	Day* of peak.	No.	Dose cc. x days.	At end Initial.	Ini- tial.	High- est.	Day* of peak.	No.	Dose cc. x days.	At end Initial.	Ini- tial.	High- est.	Day* of peak.	No.	Dose cc. x days.	At end Initial.	Ini- tial.	High- est.	Day* of peak.			
P. M.	T 670	1 x 10 i.m.	2.08	1.82	0.4	0.6	T 671	1 x 10 i.m.	1.82	1.76	0.3	2.31	3rd (18)	343	1 x 9 i.m.	1.76	2.22	1.0	4.9	9th (34)	343	5 x 8 i.m.	2.22	2.65	4.1	7.0	2d (37)
O. M.	343	10 x 2 i.m.	0.47	1.93	2.0	46.2	T 670	1 x 10 i.m.	1.03	1.90	0.6	0.8	7th (29)	T 671	1 x 10 i.m.	1.90	1.95	0.4	0.7	8th (40)	343	1 x 10 i.m.	1.95	1.85	0.5	1.2	15th (47)
T. E.	T 670	1 x 10 i.m.	2.14	2.00	0.7	0.8	T 702	1 x 10 i.m.	2.00	1.59	0.7	0.7	6th (20)	T 703	1 x 7 i.m.	1.59	1.20	0.1	0.4	3rd (27)	343	10 x 3 i.m.	1.20	..	0.4	20.0	4th (35)
G. A. C.	T 670	3 x 10 i.m.	2.18	2.09	0.8	0.9	343	3 x 12 i.m.	2.09	2.70	0.6	43.8	8th (19)	343	5 x 19 i.m.	2.70	4.22	6.7	1.2	10th (29)							
B. D.	T 702	3 x 10 i.m.	3.12	3.19	1.1	1.3	343	3 x 10 i.m.	3.40	3.46	1.0	5.1	7th (21)														
L. E.	T 703	10 x 6 i.m.	1.70	1.75	0.5	1.5	J. H. H.	10 x 10 i.m.	1.75	2.07	1.5	8.9	7th (15)														
I. G.	343	3 x 1 i.m.	2.02	2.15	1.5	1.1	T 703	3 x 9 i.m.	2.15	2.13	1.1	0.1	12th (18)	T 705	5 x 3 7 x 5 i.m.	2.06	1.86	0.1	0.5	6th (27)	343	1 x 10 i.m.	1.86	2.06	0.3	8.4	8th (37)
E. S.	343	5 x 2 3 x 5 i.m.	0.80	1.43	0.6	24.0	T 718	5 x 5 10 x 10 i.m.	2.46	2.62	0.2	0.3	4th (35)	T 703	10 x 10 I.V.	2.60	2.73	0.1	0.4	7th (49)	T 717 T 718	10 x 3 10 x 1 I.V.	2.73	2.78	0.2	0.3	5th (57)
J. Y.	J. H. H.	10 x 1 I.V.	1.15	2.59	0.8	23.0	T 717	5 x 7 10 x 6 i.m.	2.56	1.90	0.8	0.9	9th (26)	343	10 x 9 i.m.	1.90	2.33	0.6	9.5	6th (35)	343	E. N.: Period Five 10 x 5 3 x 6 i.m.	2.78	3.75	0.2	3.9	9th (68)

1-2-25 will be found in the text; "i.m." refers to intramuscular; "I.V." refers to intravenous.

* Each will be found in the text. "i.m." refers to intramuscular, "i.v." to intravenous administration.
 † The day given is that on which the highest reticulocyte count which followed administration of the stated extract was found. The number in parentheses indicates the total number of days of observation up to the time of this reticulocyte count.
 ‡ T 705 was a very irregular and probably does not represent a specific response.

from the livers of the fifth sixth (T 702) and the sixth sixth (T 703) of the gestation period. The former was ineffective in 3 cc. (Patient B. D.) as well as in 1 cc. doses (Patient T. E.) whereas the latter, tested in 4 patients, was not only ineffective in doses as high as 10 cc. intramuscularly (Patient L. E.) but even when administered intravenously in ten 10-cc. doses, was associated with no changes in the blood (Patient E. N.).

Assay of Placental Extracts. The content of anti-anemic principle in the placenta is a matter of obvious significance in regard to the suggestion^{29a} that anti-anemic principle may pass from the mother to the fetus and thus influence fetal blood formation. It has been stated that the placenta, like the brain and kidney possesses some anti-anemic potency¹⁹ but the recorded evidence is by no means conclusive. Consequently, extracts were made, in the laboratories of Eli Lilly and Company, of the placenta of pigs during the second third, the fifth sixth, and the sixth sixth of the gestation period. No precautions were taken to free the placenta of blood since the anti-anemic principle not improbably is carried in this medium.

The extracts were made by a modification of the method by which Solution Liver Extract (Lilly, 343 N.N.R.) is prepared. One cc. of solution corresponded to 5 gm. of original tissue. The following extracts were used:

T 746. A pale yellow solution made from placenta of the second third of the gestation period. Total solids 3.88 gm. per 100 cc.

T 747. Watery in appearance, with faint tinge of yellow. Total solids 1.95 gm. per 100 cc. Made from placenta of the fifth sixth of the gestation period.

T 748. Greenish solution made from placenta of the sixth sixth of the gestation period. Total solids 6.55 gm. per 100 cc.

All of these solutions were paler in color than the fetal liver extracts already described.

Results of the assay of these extracts are recorded in Table 1. T 746 was given intramuscularly to Patient I. G. in 3 doses of 5 cc. and 5 doses of 7 cc. Reticulocytes and blood counts remained unchanged. Adult liver extract, on the other hand, caused a well marked reticulocyte response in 1 cc. doses and a maximal effect was produced by 3 cc. doses.

T 747 was given to Patient J. F. in 7 doses of 5 cc. each and 6 doses of 10 cc. each. On admission this patient's condition was so grave that 1 dose of 10 cc. of adult liver extract was first given intravenously. This was followed by an increase of reticulocytes to 28% and a rise in the erythrocyte count to 2,500,000 cells. This was a submaximal response. Administration of placental extract was not commenced until 14 days following this single intravenous injection. At this time the red cell count, hemoglobin and volume of packed red cells had ceased to rise and reticulocytes had been below 2% for 4 days. During the 13 days during which placental extract was administered the erythrocyte count decreased while the reticulocytes remained unchanged. Subsequent administration of adult liver extract in 10 cc. doses was followed by a submaximal response.

Patient E. N. (Fig. 1) received extract T 748 in five 5-cc. doses and ten 10-cc. doses. As in J. F., it was necessary to treat this patient with adult liver extract before the placental extract could be used. He received a total of 30 cc. of Solution Liver Extract 343 (Lilly N.N.R.) intramuscularly, which was followed by a reticulocyte increase to 24% and a rise of the erythrocyte count to a level of 2,510,000 cells. This effect was not a maximal

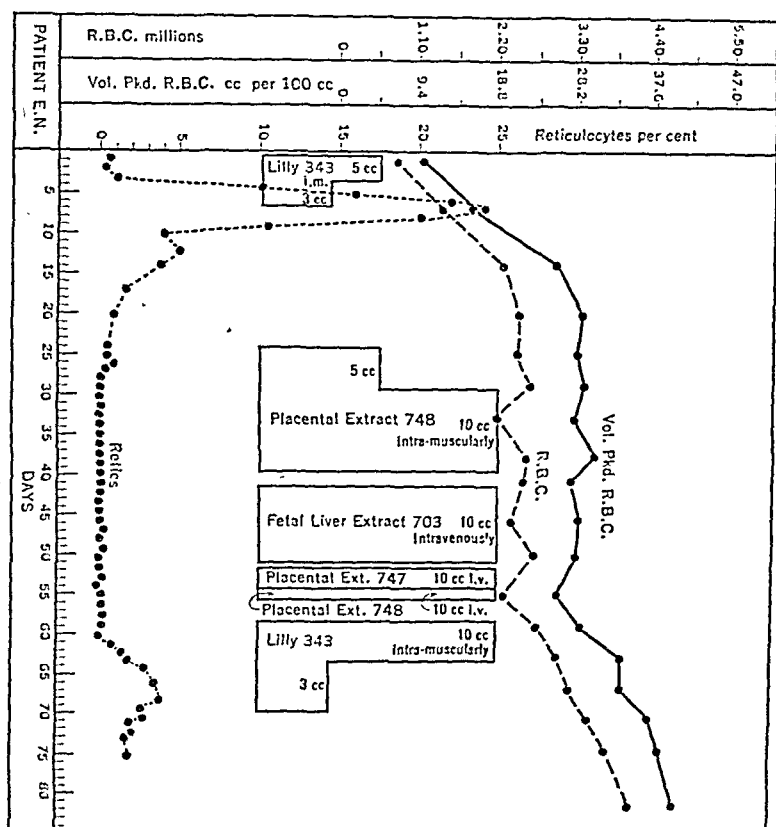


FIG. 1.—Changes in the blood of Patient E. N. as influenced by various extracts. (See also Table 1.)

response. Administration of placental extract was not commenced until 24 days following treatment with adult liver extract, by which time the reticulocytes had remained below 2% for 9 days. During the 15 days in which T 748 was administered, the reticulocytes remained at a level of 0.6 to 0.2% while the erythrocyte counts remained essentially unchanged. Following a period of 10 days during which T 703 was given intravenously without effect, T 747 was given intravenously in 3 doses of 10 cc. each and T 748 in one such dose. These injections had to be discontinued because of the patient's discomfort. Reticulocytes remained at a very low level (0.2 to 0.3%) and the erythrocyte count remained constant. Four days following the last intravenous injection, adult liver extract (Lilly, N.N.R.) was given intramuscularly. Reticulocytes promptly began to increase and the blood counts rose. The response to large doses of extract, however, was not maximal.

Like the fetal liver extracts, extracts of placenta were thus of no value whatever in the treatment of pernicious anemia. The extract of placenta of the second third of the gestation period was ineffective when 50 cc. were given intramuscularly in the course of 8 days; that made from placenta of the fifth sixth of the gestation period produced no effect on the blood when 95 cc. were given intra-

muscularly in the course of 13 days, or when 30 cc. were given intravenously in 3 days; the extract made from the placenta of the last sixth of the gestation period, though not administered under ideal circumstances, should have produced some change in the blood were any potent material present, for 125 cc. were given in the course of 15 days.

Content of Growth Factor Required by Mosquito Larvæ in Fetal and Adult Liver Extracts and in Placental Extracts. Trager²⁷ has demonstrated that the larvæ of the yellow fever mosquito (*Aedes ægypti*) require for growth an accessory food substance contained in partly purified liver extracts rich in anti-pernicious anemia principle. He has found (unpublished work) that adult pig kidney contains as much of the growth factor as pig liver, pig heart about half as much, and pig leg muscle very little. Although the substance required by the mosquito larvæ and the anti-anemic substance are not considered to be identical, they are thought to be related. Dr. Trager kindly consented to assay the fetal liver and placental extracts for this growth factor.

Because the presence of phenol which is used as a preservative in liver preparation for parenteral use interferes with the growth of mosquito larvæ, extracts corresponding in every other way to those used in patients were prepared in powdered form without preservative (Table 2). The growth data have been expressed as the product $N \times \frac{1}{T}$ in which N equals percentage of larvæ reaching the fourth instar within 9 days, and T equals the average time required

TABLE 2.—ASSAY OF LIVER AND PLACENTAL EXTRACTS FOR ANTI-ANEMIC SUBSTANCE.

Extract No.	Gestation period.	Concentration (fresh tissue per 100 cc. of solution) gm.	$N \times \frac{1}{T}$
Liver			
T 731	Second Third	100	25.0
		50	18.4
		25	9.4
T 732	Fifth Sixth	100	23.2
		50	21.1
		25	6.7
T 733	Sixth Sixth	50	23.8
		25	22.1
		12.5	5.6
343	Adult	50	21.3
		25	21.7
		12.5	19.7
		6.2	5.3
Placenta			
T 746-A	Second Third	625	5.0
		375	7.8
		250	4.4
		125	0
T 747-A	Fifth Sixth	700	2.2
		420	0
T 748-A	Sixth Sixth	330	3.3
		198	0

by these larvæ to reach the fourth instar. The maximum value for this product is 25.

The assay indicated that the placental extract had very little mosquito growth factor, even less than had pig muscle extract. Adult pig liver contained about 20 times as much growth factor as leg muscle, and about 50 to 100 times as much as placenta. In the fetal liver extracts, less growth factor was found than in adult liver extracts, there being approximately one-fourth the quantity in the extracts of livers of the second third and the fifth sixth of the gestation periods, and approximately one-half the amount in the livers of the last sixth of the gestation period as compared with adult liver extracts.

Comment. The failure to demonstrate anti-anemic principle in fetal liver may be interpreted as further evidence favoring the comparison of the fetus with the patient suffering from pernicious anemia. The hypothesis that anti-anemic principle passes from the mother to the fetus finds no support in the failure to demonstrate anti-anemic potency in placental extracts; but on the other hand, this is not necessarily to be considered as contradictory evidence; for, unless anti-anemic principle is stored in placenta, it may not be present in quantities sufficiently large to be demonstrable by our present crude methods of assay.

The significance of the presence of growth factor for mosquito larvæ in placenta and in increasing amounts in fetal livers of the successive periods of gestation, cannot be discussed at present because the relationship of this growth factor to the anti-anemic principle is not understood.

The observations recorded, do not afford direct proof of a relationship between fetal hematopoiesis and the anti-anemic principle of Castle. Numerous questions must be answered. It may be asked whether the anti-anemic principle may not be present in fetal liver in a form which is not successfully concentrated by the method employed for the preparation of extracts of adult liver. It would be of interest to know whether any of the substance is present in fetal liver which Reimann²³ and Walden and Clowes²⁴ found to be present in adult liver in a form which can be made active by incubation with gastric juice. Does the desiccated stomach of the fetus possess anti-anemic potency? Can anti-anemic principle be found in other organs of the fetus? Again, if there is a deficiency of anti-anemic principle in the fetus, will macrocytic anemia of the type seen in pernicious anemia appear in newborn animals deprived of extrinsic factor? And at what age will anti-anemic principle in demonstrable amounts be found in the livers of young animals? These and related questions are the subject of study at the present time. Until they are answered no final conclusion can be reached concerning the significance of anti-anemic principle in fetal hematopoiesis.

Summary. 1. Gastric function in the fetus and newborn is discussed. Although anatomic development is incomplete at birth, it is possible that physiologic activity may commence before this time.

2. The administration of liver extract to pregnant animals and its injection into the placenta appeared to have no effect on the blood of rabbit fetuses.

3. No anti-anemic potency was found in fetal liver extracts or in placental extracts.

4. The growth factor needed by mosquito larvæ, which is found in high concentration in extract of adult liver, was present in very small quantities in extracts of placenta and in somewhat greater amounts in fetal liver extracts.

5. The observations recorded are consistent with the hypothesis that the anti-anemic principle of Castle may play a rôle in fetal hematopoiesis, but afford no direct proof of such a relationship.

The writer wishes to express his gratitude to Eli Lilly and Company, of Indianapolis, Ind., who generously prepared the fetal liver and placental extracts, and to Mr. J. P. Scott who supervised this work. The coöperation of many physicians made the assay of extracts in patients possible. Dr. H. B. Shumacker, Jr. gave surgical aid and Mr. William Schmidt and Miss Mary Paterson rendered valuable technical assistance.

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A QUANTITATIVE CYTOLOGIC STUDY OF THE BONE MARROW OF THE ADULT DOG.

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THE clinical examination of sternal bone marrow is rapidly becoming an important diagnostic procedure in diseases of the blood and hematopoietic system. The history and technique of making sternal punctures and their application to clinical medicine have been reviewed recently by Nordenson¹⁰ and Segerdahl.¹⁵ It is assumed, of course, that the widely distributed portions of the bone marrow respond alike to any stimulus and that cytologic conditions revealed by sternal biopsy correspond essentially with those found in the marrow of other flat bones and of long bones. Alexandrov¹ (1930) studied sternal biopsies of 12 dogs, and computed the percentage distribution of the marrow cells. It is, of course, well known that changes do occur in the cellularity of the bone marrow. Marrow is spoken of as red, or cellular, and yellow, or fatty and gelatinous. Piney¹³ and Custer³ have shown that early in life the marrow of the long bones is transformed into a yellow fatty marrow, while that of the flat bones remains red; also that different bones regularly respond to increased demand at different rates. Cellularity of marrow is said to decrease with advancing years.

Although changes occur in the marrow of the shaft of long bones, wherein the active red marrow becomes yellow, there are centers or islands of active hematopoietic foci distributed throughout the fatty portions. Custer³ has shown that the cellular density in the marrow of the long bones varies enormously in even closely adjacent regions. Bone marrow is obviously a most important organ but because of its inaccessibility very little experimental work has been done on it. The bone marrow of man constitutes about 4.6% of the body weight (Mechanik⁹); of dogs about 1.9 to 2.4% (Fairman and Whipple⁴); of rabbits from 2 to 2.59% (Nye¹¹).

We undertook this comparative study of the bone marrow of the dog in order to determine whether there was any correlation in the cellular distribution in different regions of the marrow. In our study of the marrow of the rib and femur of rats,^{16a} we learned that both sites are active hematopoietic centers, and that the rib excels in erythroid production but that the femur excels in myeloid activity. When unusual stress is brought to bear on the bone marrow, as in the marked stimulation which ensues on the acute hemolytic Bartonella anemia which follows splenectomy in rats, we² found that in spite of marked erythroid stimulation in the marrow of the

femur and rib the percentage of normoblasts was always higher in the rib.

In this study we selected, in addition to the rib and the proximal portion of the femur, which are known as active centers for production of erythrocytes, the middle portion of the femur which is usually fatty. In this way the discrete cellular foci scattered throughout the yellow marrow could be compared with the distribution found in the more active red centers.

Methods. Observations on bone marrow taken from the seventh right rib, the proximal portion of the right femur (Femur I) and of the middle of the right femur (Femur II) of 35 normal adult dogs, used for other purposes in the physiologic laboratory, form the basis of this report. All animals were normal and apparently in good physical condition. They had but recently arrived at the laboratory and had not yet been fed our adequate kennel ration. Imprint preparations of bone marrow were made immediately after death, in the manner hitherto described, and were stained by Pappenheim's modification of the May-Grünwald-Giemsa technique. In addition, small pieces of bone marrow were fixed in Helly's fluid and stained according to the method of Dominici. The abundance of fat in the marrow of the middle of the femur seemed to interfere with proper staining so that many specimens were not adequately stained and the cells could not be counted satisfactorily. In each of 35 preparations of the marrow of the rib, 33 from the proximal end of the femur, and 20 from the middle of the shaft of the femur, 500 cells were counted. All data have been handled statistically. The means of the percentage distribution of all the cells in the bone marrow, together with their probable errors, sigmas, and coefficients of variation have been determined.

Krumbhaar and Custer⁷ (1935) expressed the opinion that the imprint preparations of bone marrow are not suitable for determining the relative distribution of cells, although they felt that individual cellular morphology may be best brought out by this method. They were of the opinion that cells may clump or tend to adhere to interstices of the marrow and not evenly diffuse when imprint preparations are made. We feel that this objection is probably valid when applied to the fixed cells of the marrow, such as reticulo-endothelial cells, but our experience with the imprint method has led us to conclude that it is not so clearly sustained with reference to the free cells of the marrow. When we examined the marrow of the femur and rib of splenectomized rats at intervals after splenectomy for 3 months, we found a striking similarity in the percentage distribution of free cells in the marrow of the rib and femur. Likewise, when we examined the marrow of the sternum, vertebra, rib, femur and tibia of monkeys* we found percentage distributions which were essentially alike in all five regions. If errors due to technique were common, it would seem that the percentage of free cells in these regions of marrow would be less likely to be as constant as it was. If a large number of animals is used and if the number of cells counted is sufficiently large, such errors as may be due to this method will probably be eliminated.

* Unpublished data.

TABLE 1.—PERCENTAGE DISTRIBUTION OF CELLS IN THE BONE MARROW OF ADULT DOGS.

	Myelo- blast.	Leuko- blast.	Promyelo- cyte.	Myelo- cyte.	Eosino- philic myelo- cyte.	Metamy- elocyte.	Granulo- cyte.	Eosino- phil.	Hetero- phil.	Basophil.	Normo- blast.	Lympho- cyte.	Reticulo- endo- thelial cell.	Mega- karyo- cyte.
						In the seventh right rib of 35 dogs.								
Mean	0.51 ± 0.05	1.89 ± 0.11	2.83 ± 0.17	8.93 ± 0.36	1.15 ± 0.07	15.29 ± 0.17	5.06 ± 0.43	2.83 ± 0.23	0.14 ± 0.03	0.05 ± 0.01	58.98 ± 1.12	1.24 ± 0.06	0.99 ± 0.06	0.12 ± 0.02
Signa	0.10	0.98	1.19	3.14	0.65	4.12	3.81	2.03	1.25	0.12	9.86	0.55	0.56	0.18
Coefficient of variation	78.13	51.85	52.83	35.16	56.52	26.91	75.29	71.73	178.5	210.0	16.71	44.35	56.56	150.0
						In Femur I (the proximal portion of the right femur of 33 dogs).								
Mean	0.35 ± 0.03	1.51 ± 0.10	2.04 ± 0.12	7.21 ± 0.28	1.25 ± 0.09	13.31 ± 0.55	4.36 ± 0.36	2.19 ± 0.16	0.14 ± 0.01	0.07 ± 0.05	64.95 ± 0.96	1.15 ± 0.08	1.36 ± 0.08	0.09 ± 0.02
Signa	0.23	0.81	1.03	2.40	0.74	4.07	3.05	1.38	0.31	0.39	8.18	0.64	0.68	0.13
Coefficient of variation	65.71	53.61	50.99	33.11	59.20	35.01	69.95	63.01	221.41	557.1	12.59	55.65	50.00	144.0
						In Femur II (the middle of the right femur of 20 dogs).								
Mean	0.24 ± 0.03	1.05 ± 0.11	1.68 ± 0.12	6.99 ± 0.51	1.02 ± 0.10	11.12 ± 0.55	5.39 ± 0.53	1.59 ± 0.14	0.08 ± 0.03	0.04 ± 0.01	68.02 ± 1.20	1.68 ± 0.18	1.06 ± 0.10	0.10 ± 0.02
Signa	0.23	0.72	0.81	3.39	0.65	3.67	3.50	0.93	0.21	0.09	7.96	1.19	0.64	0.13
Coefficient of variation	95.83	68.57	48.21	48.49	63.73	33.0	61.93	58.49	350.0	232.5	11.70	70.83	60.37	130.0



FIG. 1.—Myeloblast with basophilic cytoplasm, showing a fine nuclear pattern and three small visible nucleoli; stained with May-Grunwald-Giemsa stain. ($\times 1360$)



FIG. 2.—Group of myelocytes and metamyelocytes with acidophilic cytoplasm; nuclear pattern shows condensation of chromatin particles, varying stages of development are shown. ($\times 1360$)



FIG. 3.—Group of erythroid cells (included in our group of normoblasts); erythroblasts, normoblasts and normoblasts with pyknotic nuclei are shown. ($\times 1040$)

has a very fine evenly distributed amount of chromatin, and nucleoli were often present. The megakaryocytes were very large cells. Their cytoplasm was blue and contained azure granules and the nuclei were large and greatly convoluted.

The data derived from our count of the cells of the bone marrow obtained from the three regions examined have been condensed into the accompanying table (Table 1) and are graphically shown in

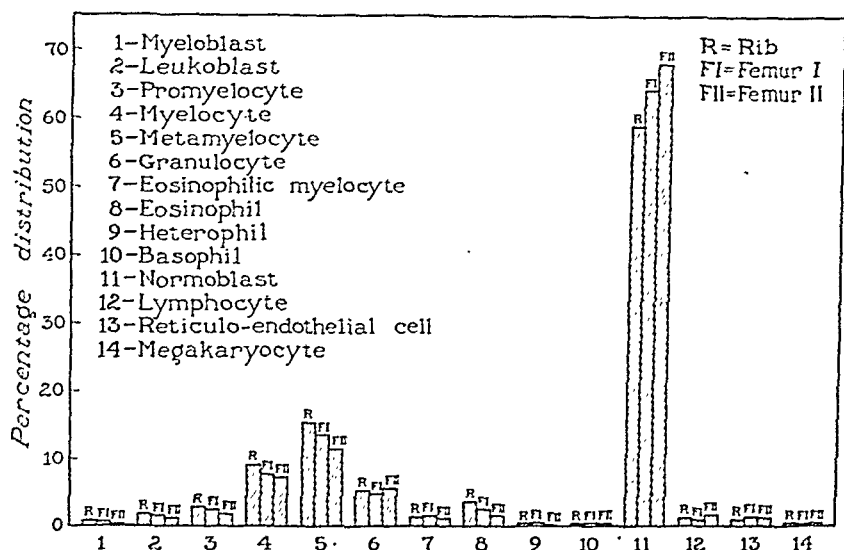


FIG. 4.—Percentage distribution of the cells encountered in the marrow obtained from three regions.

Figure 4. A survey of the table shows that there is a remarkable similarity in the percentage distribution of the different types of cells in the three regions examined, and indicates that all portions of the marrow are in general alike in their cytologic distribution. Even in preparations made from the marrow of the middle of the femur (Femur II) which is often yellow, we found essentially the same percentage distribution of the cells as we found in the marrow obtained from other regions. This indicates that the small foci seen in areas of fatty marrow are really centers of active hematopoietic proliferation. In order to appraise statistically the percentage distribution of the different cells in the marrow obtained from the three regions, we have computed the differences between the percentages found in the marrow of the rib and those found in the marrow of the proximal portion of the femur, the differences between the percentages found in the marrow of the rib and those found in the marrow of the middle portion of the femur, and the difference between the percentages found in the marrow in two regions of the femur (Table 2). In general we found a significant decrease in the percentages of the early myeloid forms in the marrow of the

middle portion of femur from those found in the marrow of the rib. There were no significant changes, however, in the percentage of mature granulocytes, in all 3 regions examined. There were significant increases in the percentage of normoblasts in the marrow obtained from the 2 sections of the femur over that found in the rib, but there was no significant difference between the percentages of normoblasts in the marrow obtained from the 2 portions of the femur.

TABLE 2.—SIGNIFICANT DIFFERENCES IN PERCENTAGE DISTRIBUTION OF CELLS IN THE BONE MARROW OF THE DOG.

Cells.	Between marrow of rib and marrow of Femur I *	Between marrow of rib and marrow of Femur II †	Between marrow of Femur I and marrow of Femur II. †
Myeloblast	0	+	0
Leukoblast	0	+	+
Promyelocyte	+	+	0
Myelocyte	+	+	0
Eosinophilic myelocyte	0	0	0
Metamyelocyte	0	+	+
Granulocyte	0	0	0
Eosinophil	0	+	+
Heterophil	0	0	0
Basophil	0	0	0
Normoblast	+	+	0
Lymphocyte	0	0	0
Reticulo-endothelial cell	+	0	0
Megakaryocyte	0	0	0

* Obtained from proximal portion of right femur.

† Obtained from middle of right femur.

There are some shifts in the relative distribution of total myeloid cells and erythroid cells that are of interest. In the marrow of the rib the percentage of myeloid cells (38.80%) was higher than it was in the marrow of the proximal end of the femur (Femur I, 32.56%) or in the marrow of the middle portion of the femur (Femur II, 29.28%). Conversely the total percentage of erythroid cells in the marrow of the rib (58.98%) was lower than it was in the marrow of the proximal end of the femur (Femur I, 64.95%) or in the marrow of the middle portion of the femur (Femur II, 68.02%).

The literature contains no statement of the myeloid-erythroid ratio in the bone marrow of the dog. This ratio has been described for the rabbit¹⁴ and for man,^{17,20} and we have described it for the white rat.^{16a} When one contrasts the myeloid-erythroid ratio in the bone marrow of these dogs with that of man, rabbit, or rat, one may note that there is a decided shift toward the erythroid side, making the ratio less than one in all the marrow of the three regions examined.

Comment. This qualitative and quantitative consideration of the cytologic constituents of bone marrow taken from three widely separated portions of the dog lead us to conclude that there is a relative identity in the cellular organization throughout. In other

words, the appraisal of the marrow of any one region will reveal within the limits of error, what the trend of the changes are in the marrow elsewhere in the body. Sabin and Doan,¹⁴ and Yamamoto,¹⁹ examined the marrow of rabbits and concluded that there were no constant differences as to the extent of erythropoiesis or granulocytopoiesis in the marrow obtained from different portions of the body. Lossen,⁸ Yamamoto,¹⁹ Williams,¹⁷ and Nordenson,¹⁰ studying the bone marrow from different regions of individuals of different age and condition, also observed a marked similarity in the cellular distribution of the marrow. Bock^{2a,b} has recently studied the function of the bone marrow in the isolated rib and thoracic vertebra, using the heart-lung preparation. He studied the cellular output in the different regions and concluded that while changes were somewhat parallel, yet granulocytopoiesis exceeded erythropoiesis in the flat bones, while the reverse was true in the long bones. Our study sustains Bock in the deduction that erythropoiesis is more marked in the long bones than it is in flat bones; in our computations the erythroid percentages were always higher than were the myeloid percentages.

The myeloid-erythroid ratio in the bone marrow of the dogs was less than one in all regions examined (Table 3). This is, of course, attributable to an increase in erythroid percentages over and above

TABLE 3.—MYELOID-ERYTHROID RATIO IN THE BONE MARROW OF THE DOG.

Source of marrow.	Myeloid cells, %.	Erythroid cells, %.	Myeloid-erythroid ratio.
Rib	38.80	58.98	0.65:1.00
Femur I*	32.56	64.95	0.50:1.00
Femur II†	29.28	68.02	0.43:1.00

* Proximal portion of femur.

† Middle portion of femur.

the relative myeloid percentages. In rats, rabbits and man the myeloid percentages whenever computed, were higher than the erythroid, and the ratio always was greater than one. Alexandrov¹ computed the percentage distribution of the cells in the sternal marrow of dogs. He did not determine the myeloid-erythroid ratio. However, from his table we have computed the total myeloid and erythroid percentages and have found that the ratio was 2.08 to 1. Sabin and Doan¹⁴ found a ratio of 2.6 to 1 in the rabbit and Young and Osgood found a ratio of 3.61 to 1 in the marrow of man. We found a ratio of 1.75 to 1 in the femur marrow of white rats. In rats in which we had induced a marked macrocytic anemia associated with a marked hepatic cirrhosis, we found myeloid-erythroid ratios less than 1.¹³ Likewise when we studied the bone marrow changes which occurred in rats after removal of the spleen, which resulted in a severe acute anemia, we also found that the myeloid-erythroid ratios were less than 1. In both of these experimental procedures we² had induced severe anemia. To compensate for this loss of erythrocytes, an erythroid stimulation was apparently induced in the bone marrow with a resultant increase in *normo-*

blasts, thus inverting the myeloid-erythroid ratio normally encountered. Young and Osgood²⁰ also observed significant changes in the myeloid-erythroid ratios in the marrow of patients with various pathologic conditions.

In the dogs there seemed to be an abnormal erythroid stimulation, for in all portions of marrow examined, the total number of normoblasts always exceeded the total number of myeloid cells. The dogs comprised an unselected group taken at random as they came to the laboratory. The mean erythrocyte count taken prior to their use was slightly in excess of 5,000,000, per c.mm. Kohanawa⁶ (1928) and Alexandrov¹ (1930) reported more than 6,000,000 erythrocytes per c.mm., and Wintrobe and others¹⁸ have reported that the normal erythrocyte count of dogs is 7,000,000 per c.mm. It thus is possible that our animals had fewer erythrocytes than might be expected in well nourished dogs maintained on adequate kennel rations. Such a slight anemia may well explain the stimulation normoblasts and may account for the exceedingly low myeloid-erythroid ratios. Oehlbeck, Robscheit-Robbins, and Whipple¹² produced an experimental anemia in dogs and found red cellular marrow throughout the entire long bones. In our animals the red marrow was restricted to the proximal portion of the femur; the middle portion was distinctly fatty, but contained small hematopoietic foci. It seems clear that the anemia induced by Oehlbeck and others¹² caused an excessive stimulation of the small foci in fatty marrow, resulting in a complete transformation into red marrow throughout.

Summary and Conclusions. This report covers a comparative study of the bone marrow of the ribs, the proximal portion of the femurs, and the middle of the femurs of 35 apparently healthy dogs. From imprint preparations of the marrow, 500 cells were counted in the marrow obtained at each site. The results are as follows:

1. Marrow obtained from all three regions showed essentially the same trend in the relative percentage distribution of the cells, indicating that a uniform mechanism regulates hematopoiesis in different portions of the widely distributed bone marrow. Consequently, the appraisal of the marrow of any one region will reveal what the trend of its cellular changes is elsewhere in the body.

2. All three regions of the bone marrow have been studied and the cellular data have been contrasted statistically.

3. Erythroid percentages exceeded myeloid percentages in all portions of marrow examined. The highest erythroid percentages were found in the isolated foci in the fatty marrow of the femur, and the lowest erythroid percentage was found in the marrow of the rib.

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THE BLOOD PICTURE BEFORE AND AFTER FEVER THERAPY BY PHYSICAL MEANS.*

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OUR problem was to determine the effects of fever, artificially produced, on the blood picture. The device used for production of artificial fever was an air-conditioned cabinet (Kettering hypertherm). It was felt that this device offered a nearly ideal method of studying the effects of fever *per se* on various human physiologic processes.

The patient lies on an air mattress in a cabinet from which the head alone protrudes. The rest of the body is enclosed in the cabinet, which is equipped with means for the very accurate control of air temperature, relative humidity and air velocity. During this particular series of studies the patient's body was exposed for periods of from 3 to 7 hours in hot, circulating humid air. The rate of circulation of the air was approximately 450 cubic feet a minute. The temperature of the air varied between 145° and 150° F., and the relative humidity was maintained constant by means of a humidistat at 40 to 45%. Samples of blood were taken from each patient immediately before and immediately after each fever treatment.

The patients under treatment during the time these studies were being conducted suffered from the following diseases: (1) Dementia præcox, (2) gonorrheal arthritis, (3) pelvic inflammatory disease (gonorrheal), (4) chronic infectious (atrophic) arthritis, (5) chorea, (6) multiple sclerosis, (7) Parkinson's syndrome (postencephalitic),

* This study was made at the Temple University Hospital, Philadelphia, Pa. I am indebted to Dr. Frank Konzelman and his technical staff for their part in the completion of the study; to Miss Grace Doyan, R.N., for technical assistance; and to Dr. W. M. Simpson of the Department of Fever Therapy Research of the Miami Valley Hospital, Dayton, Ohio, and to Mr. Charles P. Kettering, Director of the Research Laboratories of the General Motors Corporation, for the privilege of using the Kettering hypertherm.

(8) bronchial asthma and (9) trichiniasis. No attempt will be made in this paper to evaluate the effects of fever therapy on these various diseases; all that is attempted is to present a sufficiently large number of studies to give some indication of the effect of fever *per se* on the blood picture.

Table 1 shows the results obtained when capillary and venous blood counts were made on the same individual just before and just after the production of 5 hours of systemic fever at a temperature between 105° and 106° F. This study was made to determine whether or not the high capillary counts following fever were attributable to surface hyperemia, but as there was little difference between the capillary and venous counts it was concluded that the change in the capillary count was not due to surface hyperemia.

TABLE 1.—BLOOD COUNTS BEFORE AND AFTER 5 HOURS OF SUSTAINED FEVER AT 105° AND 106° F. (GENERAL AVERAGE OF 24 TREATMENTS.)

	Capillary count.		Venous count.	
	Before.	After.	Before.	After.
Leukocytes*	6,818	13,225	6,425	13,025
Erythrocytes*	3,860,000	3,780,000	3,750,000	3,710,000
Hemoglobin†	12.0	11.8	12.5	11.9
Neutrophils, %	64	80	63	82
Lymphocytes, %	24	11	24	10
Monocytes, %	4	3	3	2
Eosinophils, %	5	2	6	2
Basophils, %	1	0	1	0

* Per cubic millimeter of blood.
† Grams per 100 cc.

Since it was felt that venous counts might be slightly more accurate than capillary counts, subsequent studies were made with venous counts alone. Table 2 gives the average venous counts for 100 patients immediately before and immediately after they received sustained artificial fevers of from 3 to 7 hours' duration at temperatures ranging from 104° to 106.8° F. It will be noted that there is a marked increase in the number of leukocytes which cannot be attributed to the concentration of blood since there is no relatively large increase in the number of erythrocytes. The slight increase in the number of erythrocytes is probably due to the concentration

TABLE 2.—AVERAGE VENOUS BLOOD COUNTS OF 100 PATIENTS AFTER SUSTAINED ARTIFICIAL FEVER. (DURATION OF FEVER, 3 TO 7 HOURS; TEMPERATURE, 104° TO 106.8° F.)

	Before fever.	After fever.
Leukocytes, per c.mm.	7,125	11,269
Erythrocytes, per c.mm.	4,460,000	4,480,000
Hemoglobin, gm. per 100 cc.	13.3	13.3
Color index	0.89	0.88
Differential count, %:		
Neutrophils	56.0	81.0
Lymphocytes	38.0	15.0
Eosinophils	2.0	1.0
Monocytes	3.0	3.0
Basophils	1.0	0.0

of blood. There is a relative increase in the neutrophils and a decrease in the lymphocytes, which also indicates that the leukocytosis is not a concentration phenomena.

TABLE 3.—AVERAGE VENOUS BLOOD COUNTS OF 52 PATIENTS AFTER 5 TO 7 HOURS' SUSTAINED ARTIFICIAL FEVER. (TEMPERATURE 105° TO 106.8°F.)

	Before fever.	After fever.
Leukocytes, per c.mm.	7,094	12,470
Erythrocytes, per c.mm.	4,340,000	4,430,000
Hemoglobin, gm. per 100 cc.	13.1	13.1
Color index	0.9	0.9
Differential count, %:		
Neutrophils	59.0	83.0
Lymphocytes	35.0	13.0
Eosinophils	2.0	1.0
Monocytes	3.0	3.0
Basophils	1.0	0.0

Table 3 shows the results of similar studies of 52 patients who were given artificial fever at the higher level of temperature and time (5 to 7 hours at 105° to 106.8° F.). It will be noted that when the 48 patients whose temperatures were lower than 105° F. for periods shorter than 5 hours are excluded, the increase in leukocytes is greater and the percentage of neutrophils become higher, whereas the percentage of lymphocytes drops.

Table 4 shows the average results of studies of samples of blood from 100 patients taken before and after sustained artificial fever.

TABLE 4.—CHEMICAL CONSTITUENTS OF BLOOD OF 100 PATIENTS AFTER SUSTAINED ARTIFICIAL FEVER FOR 3 TO 7 HOURS. (TEMPERATURE, 104° TO 106.8° F.)

	Milligrams per 100 cc. of whole blood.						Carbon dioxide combining power of blood, vol. %.	
	Chlorides (oral administration of 2 to 3 liters of 0.6% solution of sodium chloride).		Sugar.		Urea nitrogen.			
	Before.	After.	Before.	After.	Before.	After.	Before.	After.
Average in 52 cases (fever greater than 105° F.)	463	466	101.2	110.8	10.1	14.1	53	42
Average in 48 cases (fever greater than 104° F.)	462	465	95.4	99.3	12.3	14.6	57	49
Average in 100 cases (fever from 104° to 106.8° F.)	462	466	97.8	104.1	11.2	14.5	56	46
	Sedimentation time, min.		Sedimentation rate, mm.					
	Before.	After.	Before.	After.				
Average in 100 cases (fever from 104° to 106.8° F.)	50.0	53.5	12.3	13.0				

Temperatures were raised to 104° to 106.8° F. by means of the air-conditioned cabinet and were sustained at these levels from 3 to 7 hours. Determinations were made of the blood chlorides, blood sugar, urea nitrogen, carbon dioxide combining power and the sedimentation time. Because of the previously reported marked drop in blood chlorides due to loss of chlorides in perspiration, all of these patients were given 2 to 3 liters of a 0.6% solution of ice-cold sodium chloride during treatment. It will be seen that this amount of saline solution was sufficient to prevent any drop in the blood chlorides; in fact, under these circumstances, there was a slight increase. The increase in blood sugar and urea nitrogen are probably due to concentration of the blood. The changes in the carbon dioxide combining power of the blood and sedimentation time are of little significance but are included for the sake of completeness.

TABLE 5.—TENDENCY TOWARD AN INCREASE IN THE NUMBER OF NEUTROPHILS, A DECREASE IN MONONUCLEAR CELLS AND THE NEGLIGIBLE SHIFT TOWARD THE LEFT FOLLOWING SUSTAINED ARTIFICIAL FEVER AT 104° TO 107° F. FOR FROM 3 TO 7 HOURS IN AN AIR-CONDITIONED CABINET.

Percentage of neutrophils.								
Case.	No of tests.	Before fever.			After fever.			Shift toward
		Im-mature.	Mature.	Total.	Im-mature.	Mature.	Total.	
1	8	28 8	24 5	53 3	44 8	38.1	82 9	Right
2	3	40.0	18 0	58 0	57 7	9 4	67.1	Left
3	5	22 2	25 8	48 0	42 25	43 0	85 25	Left
4	8	32.5	31 1	63.6	40 4	42 8	83.2	Right
5	4	6 2	55.8	62.0	6 5	77.7	84 2	Right
6	1	2 0	40 0	42 0	17 0	67 0	84 0	Left
7	9	16 0	30 1	46 1	28.9	46.2	75 1	Left
8	8	15 5	24 5	40 1	33 0	40 2	73 2	Left
9	1	5 5	48 5	54 0	6 0	82 0	88 0	Right
10	1	25 0	21 0	46 0	41 0	40 0	81 0	Right
11	1	11 0	62 0	73 0	22 0	63 0	85 0	Left
12	1	1 0	51 0	52 0	5 0	81 0	86 0	Left
13	8	24 0	29 2	53 2	40 8	42 14	82 9	Left
14	10	23 8	30 2	54 0	32 6	47 1	79 75	Right
15	4	33 8	24 2	58.0	53 05	33 8	86.85	Left
Av. of 72 tests		19 16	34 39	53.55	31 40	50 23	81.63	Left
		Filament. Non-filament		Filament. Non-filament.				
Per cent		35 76 64 23		38 46 61 53				

Table 5 gives the blood counts of 72 patients who were treated under the conditions just mentioned. This table, while showing a slight shift toward the left for the average of the 72 studies, nevertheless does not show the marked shift to the left which is present when fever is produced artificially by means of malarial inoculations. The difference of 2.7% shown in this table between the filamented and non-filamented forms before and after treatment is so slight that it may be attributed simply to statistical error. The very slight shift toward the left may therefore be considered as negligible.

Owing to the fact that the particular method which I have used for studying the blood picture has not taken into consideration the possibility of changes at other times during the period of fever and after the period of fever, and owing to the fact that Dr. Malcolm Hargraves¹ has made a special study of this particular phase of the blood picture in artificial fever therapy, I have asked Dr. Hargraves to add to this presentation a note which points out the discrepancies in my studies as compared with his own studies and makes the entire subject a little more clear.

Comment by Hargraves. In this, as in all problems, there are several lines of approach which may be used in attempting the solution. Since we have made the relationship of fever to the hemopoietic equilibrium one of our chief interests during the last few years, and since our line of approach has been somewhat different from the one employed by Dr. Krusen, he has very kindly asked us to append to his paper the following comment:

Dr. Krusen's figures on total leukocyte and differential count changes, as well as filament-non-filament ratios, are quite in accord with our work when interpreted in the light of that work. That is, Dr. Krusen's figures do not take into account the succession of changes which occur for the next 20 hours following the onset of fever and consequently, in themselves, might be misleading and mask the true postfebrile blood picture. If this period is studied with multiple, serial counts, say at intervals of a half hour, a rather constant response will be found. This response is so constant that we feel that the term "febrile hemogram" is justified. It is characterized by a postfebrile leukocytosis, the duration and extent of which is an individual affair and bears a relationship to the duration and height of fever. The peak of leukocytosis is dependent on a polymorphonuclear increase and often goes as high as, or higher than, 40,000 leukocytes per c.mm. total white blood cell count. It is here that the younger cells, as shown by a changing filament-non-filament ratio, are increased; this is evidence of bone-marrow delivery and not of a redistribution phenomenon. As the polymorphonuclear peak declines, the total count is usually sustained, or partially sustained, by an influx of monocytes. The last cell to reappear in numbers is the lymphocyte, which usually assumes lymphopenic proportions during the episode of fever.

With this picture in mind it can be seen that Dr. Krusen's figures are correct for the time of sampling, but that they usually miss the peaks of response which would have given a much greater contrast to his determinations before and after fever than his tables now indicate.

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PLASMA PROTHROMBIN LEVEL IN NORMAL INFANCY AND IN HEMORRHAGIC DISEASE OF THE NEWBORN*

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IN previous work³ we have developed a method for the titration of prothrombin in plasma. The older methods, such as prothrombin time, gave results which are known to be dependent upon many variables, and to be highly unreliable for the quantitative measurement of prothrombin. With the aid of the new technique we found that in normal adult dogs the prothrombin level varies but little from dog to dog and from day to day. More recently we have found that in man the adult prothrombin level is also rather constant but somewhat lower than in the dog. The present study shows that the value for newborn infants is only about one-fourth that of the adult human value. The rise to the adult level requires about a year.

The prothrombin level of the newborn is not only low but is also somewhat variable from case to case—facts of great interest in connection with the bleeding tendency so often seen in newborn babies. That low prothrombin values can be of importance in hemorrhagic disease of the newborn is shown in a case presented below. Prothrombin was found to be almost completely absent during the period of bleeding. Following intravenous transfusion the bleeding ceased and the prothrombin rose to and was maintained at the level seen in normal babies.

Case Abstracts of Normal Babies. Cases 1 to 9, from Obstetrical Service. Mothers' physical and laboratory examinations, including Wassermann reactions, negative. Course of pregnancy normal in all cases, except for occasional mild attacks of nausea. Routine ethylene anesthesia of less than 1 hour in each case. Babies took food normally.

Cases 10 to 19 from Pediatrics Metabolism Ward. Wassermann negative in all cases. Fed abundant milk formula diet. Cases 10, 13, 14, 18 and 19 received moderately large supplementary amounts of vitamins A and D; 16 and 17 received rather low amounts of A and D; 11 and 12 moderately low amounts of A and moderate amounts of D; 15 rather low amounts of A and very large amounts of D. All babies followed the normal weight curve and appeared to be in excellent health. Blood taken from the jugular vein or fontanelle in all cases.

* This work was made possible through the generous coöperation of Drs. E. D. Plass, John H. Randall, and Warren W. Tucker of the Department of Obstetrics; of Drs. Philip C. Jeans, Julian D. Boyd, Genevieve Stearns, and Charlotte Fisk of the Department of Pediatrics; and of Dr. Arthur Steindler of the Department of Orthopedics.

Cases 20 and 21 from the Orthopedic Service. Brought in for check-up on treatment of clubfoot.

CASE 1 (M-13736). Newborn baby boy. Weight, 4065 gm.; length, 51 cm. Mother, 33 years; 6 previous pregnancies, no miscarriages. Expected date May 19; actual delivery May 29. Labor 5 hours. Plasma prothrombin (cord blood) 14% of normal adult control plasma value.

CASE 2 (M-13266). Newborn baby boy. Weight, 3958 gm.; length, 50 cm. Mother, 32 years; 5 previous pregnancies, including 1 miscarriage. Expected date April 15; actual delivery May 15. Labor 3 hours. Plasma prothrombin (cord blood) 19% of adult control value.

CASE 3 (M-13917). Newborn baby girl, mildly asphyxiated. Weight, 3000 gm.; length, 49 cm. Mother, 28 years; primipara. Expected date June 21; actual delivery June 4. Labor 24 hours, low forceps. Plasma prothrombin (cord blood) 24% of adult control value.

CASE 4 (M-13738). Newborn baby girl. Weight, 3548 gm.; length, 49 cm. Mother, 19 years; 1 previous full term pregnancy. Expected date May 20; actual delivery May 29. Labor 6 hours. Plasma prothrombin (cord blood) 25% of adult control value. Infant blood taken by venipuncture 8 days later showed plasma prothrombin to be 44% of the adult value.

CASE 5 (M-13737). Newborn baby girl. Weight, 2910 gm.; length, 51 cm. Mother, 27 years; 2 previous pregnancies, including 1 miscarriage. Expected date May 7; actual delivery May 29. Labor 6 hours. Plasma prothrombin (cord blood) 28% of adult control value.

CASE 6 (M-13270). Newborn baby girl. Weight, 2868 gm.; length, 47 cm. Mother, 24 years; primipara. Expected date April 15; actual delivery May 15. Labor 28 hours. Plasma prothrombin (cord blood) 27% of adult control value. Blood by venipuncture on May 20, 5 days after birth, showed the plasma prothrombin to be 36% of the adult value.

CASE 7 (M-13390). Newborn baby girl. Weight, 3000 gm.; length, 48 cm. Mother, 22 years; primipara. Expected date May 25; actual delivery May 19. Labor 24 hours. Plasma prothrombin (cord blood) 36% of adult control value.

CASE 8 (M-13916). Newborn baby girl. Weight, 3006 gm.; length, 47 cm. Mother, 20 years; primipara. Expected date June 15; actual delivery June 4. Labor 24 hours. Plasma prothrombin (cord blood) 39% of adult control value.

CASE 9 (M-13441). Baby boy. Birth weight, 3124 gm.; length, 48 cm. Mother, 21 years; 1 previous pregnancy. Expected date May 27; actual delivery May 20. Labor 6 hours. Baby's blood by venipuncture May 28, 8 days after birth, showed plasma prothrombin to be 27% of the adult value.

CASE 10 (M-13519). Baby girl of 11 days weighing 3200 gm. Plasma prothrombin 37% of adult control value.

CASE 11 (M-11951). Baby boy of 7 weeks, weighing 4650 gm. (3780 at birth). Plasma prothrombin 42% of adult control value.

CASE 12 (M-11785). Baby girl of 8 weeks; weight, 4450 gm. (3202 at birth). Plasma prothrombin 42% of adult control value.

CASE 13 (M-11136). Baby girl of 11 weeks; weight, 5375 gm. (3178 at birth). Plasma prothrombin 61% of adult control value.

CASE 14 (M-10963). Baby girl of 12 weeks; weight, 4700 gm. (2880 at birth). Plasma prothrombin 61% of adult control value.

CASE 15 (M-7819). Baby girl of 21 weeks; weight, 6030 gm. (3204 at birth). Baby isolated from mother, who has advanced chronic pulmonary tuberculosis. Plasma prothrombin 68% of adult control value.

CASE 16 (M-6586). Baby girl of 28 weeks; weight, 6825 gm. (4000 at birth). Plasma prothrombin 77% of adult control value.

CASE 17 (M-5586). Baby girl of 30 weeks; weight, 6520 gm. (2786 at birth). Plasma prothrombin 79% of adult control value.

CASE 18 (M-4017). Baby boy of 38 weeks; weight, 8550 gm. (3800 at birth). Plasma prothrombin 88% of adult control value.

CASE 19 (M-511). Baby boy of 47 weeks; weight, 9950 gm. (3968 at birth). Plasma prothrombin 100% of adult control value.

CASE 20 (M-8238). Baby girl of 38 weeks; weight, 8800 gm. Congenital right clubfoot, corrected by manipulation and casts applied several months ago. Physical and laboratory examinations otherwise negative. Plasma prothrombin 85% of adult control value.

CASE 21 (M-1655). Baby girl of 42 weeks; weight, 9765 gm. Congenital bilateral clubfoot, corrected during the past 6 months by manipulation, casts and lengthening of Achilles tendons. Otherwise normal on physical and laboratory examinations. Plasma prothrombin 99% of adult control value.

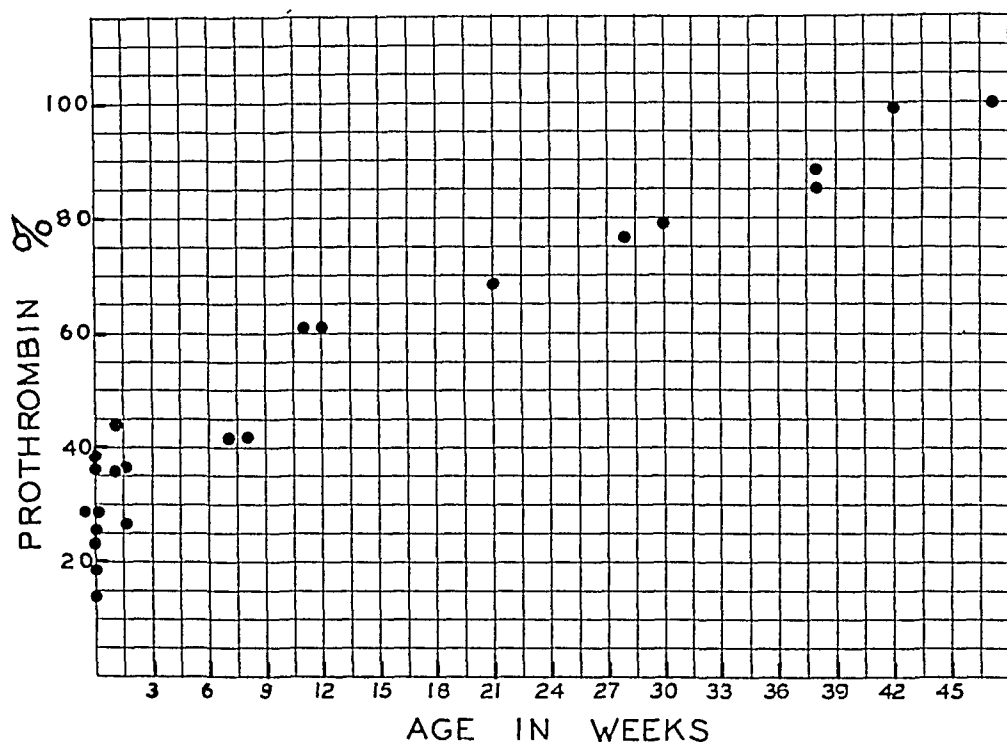


CHART I.—PLASMA PROTHROMBIN IN INFANTS OF VARIOUS AGES.

Chart I shows the plasma prothrombin values of the 21 normal infants of varying ages. The level characteristic of adult plasma is reached at the end of the eleventh or twelfth month. During the last 9 months of this period the rise is gradual, with remarkably little individual deviation from the general upward trend. The regulating mechanism appears to have become well established. In the first month of life the prothrombin values are subject to much greater variation. In the 8 newborn infants studied, the values ranged between 14 and 39% of the adult level. One of the 8 (Case 4) was bled again at the end of 8 days. The prothrombin had risen from the initial value of 25% up to 44%. A second infant (Case 6) rose from 28% up to 36% in 5 days. These 2 cases supple-

ment the statistical evidence of a steady rise in prothrombin toward adult levels.

Such variability as is present in the prothrombin level in the present series is not very clearly associated with such factors as sex, size of infant, length of gestation, or the length of labor. The series is too small, however, to rule out lesser degrees of correlation. The older infants in the Metabolism Ward were being given varying amounts of vitamins in studies being directed by Dr. Philip C. Jeans. A number of these infants, serving as controls, received average amounts of vitamins A and D. Two of them (Cases 16 and 17) received only the vitamins contained in the milk. Case 15 received very large amounts of vitamin D (10 drops viosterol 3 times a day). These dietary variations clearly had no effect upon the prothrombin level.

The earlier work on blood clotting in normal infants includes many studies on bleeding time and clotting time. The results vary somewhat with different workers, but rarely differ significantly from adult figures. The so-called prothrombin time (the clotting time of recalcified oxalated plasma) is also within normal adult limits. This clotting time, like the clotting time of whole blood, is dependent upon the amounts of antithrombin, prothrombin, and fibrinogen present. It also depends in a very striking way upon the amount of contamination by tissue juice and ruptured platelets. As we have shown,^{3,2} only a relatively small part of the prothrombin normally present is needed to give a normal clotting time, provided the other clotting factors are properly adjusted. The prothrombin time, dependent as it is on many variables, is not a reliable measure of the prothrombin present, and conclusions based upon it must be discounted.

We have studied the plasma prothrombin level in a number of pregnant women and have found no significant deviation from that of non-pregnant women. Two cases studied shortly before delivery showed values of 100 and 93% of the non-pregnant control. Three, each taken a few minutes after delivery, were 110, 99, and 98%. It is evident that the fetal prothrombin level lacks the stability of that of the mother, and that the two levels are not related in any very simple way.

A Case of Hemorrhagic Disease of the Newborn. (M-13179). A patient of Dr. John H. Randall. Mother a primipara. Child had congenital heart disease recognized since age of 4. No frank hemorrhages; occasional epistaxis in childhood; none since. Expected date of delivery June 8. Vomiting began April 15, increased in severity. Patient was put on a diet low in protein and high in fruits and vegetables. She was given glucose intravenously. She had some luminal as sedative. No other drugs. Vomitus showed some unexplained coffee-ground material and traces of fresh blood at times. Examination May 13 showed moderate edema of ankles, marked albuminuria. No pyuria, no hematuria. Blood pressure, 154/90; white count, 16,350; normal differential; red count, 5.6 million; Wassermann test negative. No fever during period of observation. Due

to evidence of toxemia and renal involvement, a Cesarean section was carried out under local novocaine anesthesia on May 13. Operation uneventful except for some excess bleeding from uterine incision. Rapid recovery. On discharge May 24, she still had albuminuria and blood pressure of 150/80.

The infant, a female, was moderately cyanotic. Weight, 2792 gm.; length, 46 cm. Did well until its cord clamp came off on the fifth day, May 16. Following this there was oozing of blood from the cord stump. The cord was sutured on 3 occasions on May 17, and each time the oozing was only temporarily checked. In an effort to stop the bleeding, baby was given 20 cc. thromboplastin (Squibb) in divided doses subcutaneously on the 19th. Later in the evening 32 cc. of blood were given intramuscularly, and approximately 50 cc. of 5% coagulin (Ciba) were administered orally in divided doses during the course of the night. Also 10 cc. coagulin subcutaneously. Treatment ineffective. Blood oozed from puncture wounds where coagulants were injected and from stab wounds in heel from which blood was drawn for studies preparatory to transfusion. At 1.45 p.m. May 20, 100 cc. citrate blood were given intravenously. Bleeding ceased promptly. Some inflammation incident to placing sutures about the umbilicus cleared up in the next few days and the baby showed uneventful recovery and was discharged June 7. Temperature normal throughout. Infant diet May 13 and 14 was diluted cow's milk plus Karo; May 15 to 28, breast milk; diluted evaporated milk plus dextrimaltose and lactic acid thereafter.

Diagnoses: Maternal congenital heart disease; maternal toxemia with renal involvement; Cesarean section; hemorrhagic disease of the newborn, cured by transfusion.

Venous blood was taken from the antecubital fossa May 20, immediately before giving the transfusion. Hematocrit showed 17.5% cell volume. The plasma fibrin by the method of Jones and Smith³ was 392 mg. per 100 cc. The prothrombin was too low for accurate estimation. It was clearly below 5% of the normal adult value. The antithrombic activity of the oxalate plasma was determined by incubating the plasma in varying dilutions with thrombin. After a set interval the amount of thrombin left was tested by adding fibrinogen. As a control, a series of normal plasma dilutions was tested against the thrombin. By comparing the two curves the antithrombic potency in this case was found to be approximately twice that of the normal adult control plasma.

A second blood sample taken 10 days later showed a cell volume of 42.9% and the prothrombin titer was 38% of the adult control plasma.

The mother's hematocrit May 21 showed 32% cells; the prothrombin was 100% of normal.

July 3, infant's hematocrit showed 32% cells. The plasma prothrombin was 47% of the normal adult control value. The antithrombin was within normal limits.

This patient, a primipara, 29 years old, had congenital heart disease and nephritic toxemia. She was delivered by Cesarean section 3 weeks prematurely. The baby appeared normal until the fifth day, when the cord came off and blood began to ooze from the stump. This continued for 3 days, at the end of which time the hematocrit showed 17.5% cells. The prothrombin at this time was almost completely absent. A further abnormality consisted of a moderate increase in the antithrombic activity of the plasma. The plasma fibrin level was normal. Transfusion brought about prompt cessation of bleeding. Since adult blood is rich in pro-

thrombin, the transfusion was sufficient to raise the prothrombin level to about 25 or 30% of the adult value. This level, as we have shown, is normal for infants of this age. The ability of the infant to maintain such normal levels was shown by an analysis made 10 days later, at which time the prothrombin was 38% of the normal adult value. Forty-four days after transfusion it was 47%.

This case with its response to treatment supplies sound theoretical grounds for the well-known benefits of transfusion. The case also points strongly to the conclusion that lowered prothrombin is the essential cause of bleeding in certain cases of hemorrhagic disease of the newborn. The earlier qualitative work of Whipple,⁴ pointing to this same conclusion, has not received general acceptance, probably because his analyses were made on blood drawn at autopsy. Several investigators more recently have given conflicting opinions concerning this disease, basing their conclusions upon the prothrombin time. As we have stated, this method cannot be expected to give significant figures regarding the amount of prothrombin present.

Our data do not permit an opinion regarding the ultimate cause of hemorrhagic disease of the newborn. It may well be that some factor occurring in the first few days of life reduces the normally low prothrombin to the bleeding level which we observed. It is equally possible that an occasional infant is born with exceptionally low values. The incidence of hemorrhagic disease of the newborn is said to be about 1 in 200 births. In a large series it might be that a few infants would reach the danger level. The great variability shown in our series of newborn infants points to such a possibility. This variability and an occasional tendency to bleed may both be the result of pre-natal factors of unknown nature.

Summary. The plasma prothrombin level in infancy was studied with the aid of a quantitative titration procedure. The level in normal newborn babies varies in this series between 14 and 39% of the level found in normal adult plasma. The prothrombin level rises gradually during subsequent months and reaches the adult level at the end of about a year. After the first few weeks of life the individual cases show very little deviation from the curve plotted through the entire group.

A case of hemorrhagic disease of the newborn studied showed the plasma prothrombin to be less than 5% of normal adult values. The antithrombic activity of the plasma was somewhat excessive, but the plasma fibrin was normal. Intravenous transfusion of blood resulted in prompt cessation of bleeding. The plasma prothrombin studied 10 and 44 days later was found to be up to the normal values for infants of that age.

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AUTOPSY INCIDENCE OF CHOLELITHIASIS.

BASED ON RECORDS OF INSTITUTE OF PATHOLOGY, WESTERN
RESERVE UNIVERSITY AND UNIVERSITY HOSPITALS,
CLEVELAND, OHIO.

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In an article entitled, "Cholelithiasis in the Korean,"² the writer made a comparison of the autopsy incidence of cholelithiasis among Koreans with that among other races. A summary was given of 2800 autopsies (February 2, 1898, to June 2, 1927) from the records of the Department of Pathology of Lakeside Hospital, Cleveland, Ohio. To this series is now added the results obtained in 2000 autopsies (June 3, 1927, to July 21, 1935), performed at the Institute of Pathology, Western Reserve University and University Hospitals, Cleveland, Ohio. Table 1 gives a summary of both these

TABLE 1.—AUTOPSY INCIDENCE OF CHOLELITHIASIS, BASED ON RECORDS OF
LAKESIDE AND UNIVERSITY HOSPITALS.
(February 2, 1898, to July 21, 1935—4800 Autopsies).

Age (years).	White.								
	Male.			Female.			Total.		
	No. of autopsies.	No. with gall stones.	Per cent.	No. of autopsies.	No. with gall stones.	Per cent.	No. of autopsies.	No. with gall stones.	Per cent.
0-10	438	0	0.00	334	0	0.00	772	0	0.00
11-20	113	1	0.88	65	1	1.54	178	2	1.12
21-30	238	6	2.52	183	9	4.92	421	15	3.56
31-40	375	9	2.40	257	19	7.39	632	28	4.43
41-50	492	31	6.30	228	38	16.66	720	69	9.58
51-60	394	42	10.66	168	38	22.62	562	80	14.23
61-70	232	35	15.09	105	26	24.76	337	61	18.10
71-80	102	14	13.73	41	11	26.83	143	25	17.48
81-90	8	0	0.00	6	3	50.00	14	3	21.43
91-100	0	0	0.00	0	0	0.00	0	0	0.00
Total	2392	138	5.77	1387	145	10.45	3779	283	7.49
	Negro.								
	No. of autopsies.	No. with gall stones.	Per cent.	No. of autopsies.	No. with gall stones.	Per cent.	No. of autopsies.	No. with gall stones.	Per cent.
	No. of autopsies.	No. with gall stones.	Per cent.	No. of autopsies.	No. with gall stones.	Per cent.	No. of autopsies.	No. with gall stones.	Per cent.
0-10	74	0	0.00	86	0	0.00	160	0	0.00
11-20	22	0	0.00	20	0	0.00	42	0	0.00
21-30	94	0	0.00	104	2	1.92	198	2	1.01
31-40	143	2	1.40	114	8	7.02	257	10	3.89
41-50	115	4	3.48	78	11	14.10	193	15	7.77
51-60	81	10	12.35	41	9	21.95	122	19	15.57
61-70	18	1	5.56	9	3	33.33	27	4	14.81
71-80	9	0	0.00	8	1	12.50	17	1	5.88
81-90	3	0	0.00	1	1	100.00	4	1	25.00
91-100	1	0	0.00	0	0	0.00	1	0	0.00
Total	560	17	3.04	461	35	7.60	1021	52	5.09
Grand Total	2952	155	5.25	1848	180	9.73	4800	335	6.98

groups, or a total of 4800 autopsies, arranged in age, sex and color groups with the number of cases having gall stones and the percentage frequency in each group. Table 2 shows the number of cases

of gall stones in each decade, with total percentages, regardless of sex and color.

TABLE 2.—AUTOPSY INCIDENCE OF CHOLELITHIASIS REGARDLESS OF SEX AND COLOR.

Age (years).	No. of autopsies.	No. with gall stones.	Per cent.
0 to 10	932	0	0.00
11 to 20	220	2	0.91
21 to 30	619	17	2.75
31 to 40	889	38	4.27
41 to 50	913	84	9.20
51 to 60	684	99	14.47
61 to 70	364	65	17.86
71 to 80	160	26	16.25
81 to 90	18	4	22.22
91 to 100	1	0	0.00
Total	4800	335	6.98

Mosher,³ in 1901, examined the records of 1655 complete autopsies from the Pathological Department of the Johns Hopkins Hospital. Of the 1655 patients, 1037 were males and 618 females; 634 were black and 1018 were white; the color of the remaining 3 cases was not given. In 115 cases (6.94%) gall stones were present.

Hamilton¹ (1925-1929) analyzed the records of 1000 autopsies performed at the Adelaide Hospital, Adelaide, Australia. Among the 1000 autopsies, of which 675 were on males and 325 on females, gall stones were found in 106 (10.6%).

Ophüls,⁴ among 3000 autopsies performed during the years 1900 to 1923, mostly at the Lane and San Francisco Hospitals, found 214 cases of gall stones (7.1%). Of 206 patients with gall stones, 139 were men (5.86% of all males) and 67 women (10.65% of all females).

In our own series of 4800 autopsies (Table 1) gall stones were present in 335 cases (6.98%). Of the 335 patients with gall stones, 155 were men (5.25% of all males) and 180 women (9.73% of all females).

Summary. An analysis of our autopsy incidence of cholelithiasis shows:

1. Gall stones are rarely found in persons under 20 years of age; only twice in 4800 autopsies.

2. There is a gradual increase in frequency from 20 years of age.

3. Gall stones are found more frequently in the white race (7.49% than in the negro race (5.09%).

4. Gall stones are found more frequently among females (9.73%: white, 10.45%; negro, 7.6%) than among males (5.25%: white, 5.77%; negro, 3.04%).

I wish to express my appreciation to Dr. Howard T. Karsner for the use of the records of the Institute of Pathology, Western Reserve University.

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STUDIES OF GALL BLADDER FUNCTION.

XIV. ABSORPTION OF SODIUM TETRAIODOPHENOLPHTHALEIN
FROM THE NORMAL AND DAMAGED GALL BLADDER.*

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RECENT studies of the physiology of the gall bladder have concerned themselves for the most part with the study of the absorption and excretion by the gall bladder of the normal constituents of the bile. The method of cholecystography recommended by Graham, Cole and Copher² more than 10 years ago, depends upon the use of sodium tetraiodophenolphthalein. It is, therefore, important that the effect of the normal and damaged gall bladder upon this salt be known.

The failure to make the gall bladder visible† in cholecystography is interpreted to be due to: *a*, failure of the absorption of the dye from the gastro-intestinal tract; *b*, failure of the liver to excrete the dye in adequate amounts; *c*, incompetence of the sphincter of Oddi; *d*, obstruction of the cystic duct; or *e*, a degree of cholecystitis which does not permit of concentration of the dye in the gall bladder. Much clinical as well as experimental evidence confirms these interpretations.⁴ The lack of concentration of the dye in the gall bladder in cholecystitis is adequately accounted for by the evidence that water is not absorbed by the damaged gall bladder or if so, is absorbed in very small amounts.⁶

Another possibility which has been suggested as an explanation for the failure to make the gall bladder visible after dye administration is the rapidity with which it may be absorbed by the damaged gall bladder.⁴ This possibility is strengthened by the work of Igwanaga³ who reported that bacterial or mechanical inflammation of the gall bladder mucosa increases the rate of absorption of phenolsulphonphthalein, methylene blue and indigo-carmin. Likewise, Winkenwerder⁹ found that slight injury of the gall bladder wall resulted in the rapid absorption of the Prussian blue reagents. Experiments on the absorption of sodium tetraiodophenolphthalein from the gall bladder were reported from this laboratory by Johnston⁵ in 1931. His experiments refuted the previously advanced concept⁸ that the sudden disappearance of the gall bladder shadow following a fatty meal, in clinical cholecystography, was

* Aided by a grant from the Josiah Macy, Jr., Foundation.

† The Editor has taken the liberty of changing the obviously incorrect term "visualized." We try to avoid this solecism in this journal in spite of its present widespread usage, in the hope that a better term may eventually be substituted.

due to absorption of the salt through the gall bladder wall, rather than an expulsion of it through the cystic duct. He showed that a fatty meal did not increase the amount of dye absorbed from the gall bladder bile. In a series of 6 dogs, when the salt was injected into the gall bladder by a needle with the cystic duct occluded without injury to the blood or lymph vessels, from 26 to 51 % of the salt was recovered from the gall bladder after 24 hours.

If it can be shown that the damaged gall bladder absorbs sodium tetraiodophenolphthalein more rapidly than the normal gall bladder, it is reasonable to suppose that this may in part account for the failure to make the diseased gall bladder visible when using the Graham-Cole method. Experiments were, therefore, devised to test this.

Our initial experiments were conducted with a method similar to that used by Johnston.⁵ Essentially, this consisted of dissolving the sodium tetraiodophenolphthalein in gall bladder or hepatic bile and injecting this solution into the gall bladder lumen by needle puncture after preliminary occlusion of the cystic duct.

Histologic examination of the gall bladder removed from animals in which the dye had been so introduced showed a surprising degree of change of the gall bladder mucous membrane. The cellular change was of such extent that it was obvious that we were not dealing with a normal membrane (Fig. 2).

It was found that in those instances where the cystic vessels did not lie on the cystic duct, the duct could be ligated without the development of histologic changes in the gall bladder wall. The changes observed after injection of the dye must, therefore, have been due to the dye itself.

In the course of these experiments it was observed that when sodium tetraiodophenolphthalein was given intravenously, the hepatic and gall bladder bile did not change its normal appearance. On the other hand, when the salt was dissolved directly in the gall bladder or hepatic bile in the same quantities as those found after intravenous injection, the bile developed a dirty bluish tinge. It seems obvious then, that sodium tetraiodophenolphthalein is not excreted in the bile in the same form as it is given intravenously. It was, therefore, necessary to devise a new method for studying the absorption of sodium tetraiodophenolphthalein from the gall bladder so that at the conclusion of the experiment the mucosa would be of normal appearance.

Absorption of Sodium Tetraiodophenolphthalein from the Normal Gall Bladder. The dye was given to a dog intravenously, and either the hepatic bile was collected for the following 24 hours or the gall bladder was removed after starving the dog for 24 hours, in order to get the dye in a more concentrated form. An aliquot of the bile was analyzed for its iodine content. A known amount of this bile containing the dye was then injected into the gall bladder of a second



FIG. 1.—*Normal gall bladder.* Bile from a dog previously given sodium tetraiodophenolphthalein was injected into this gall bladder by needle puncture, the cystic duct having been ligated. After 24 hours the gall bladder appeared grossly and microscopically normal.



FIG. 2.—*Damaged gall bladder.* Sodium tetraiodophenolphthalein dissolved in bile was injected into this gall bladder by needle puncture, the cystic duct having been ligated. After 24 hours the damage to the mucous membrane was questionable grossly but evident microscopically.

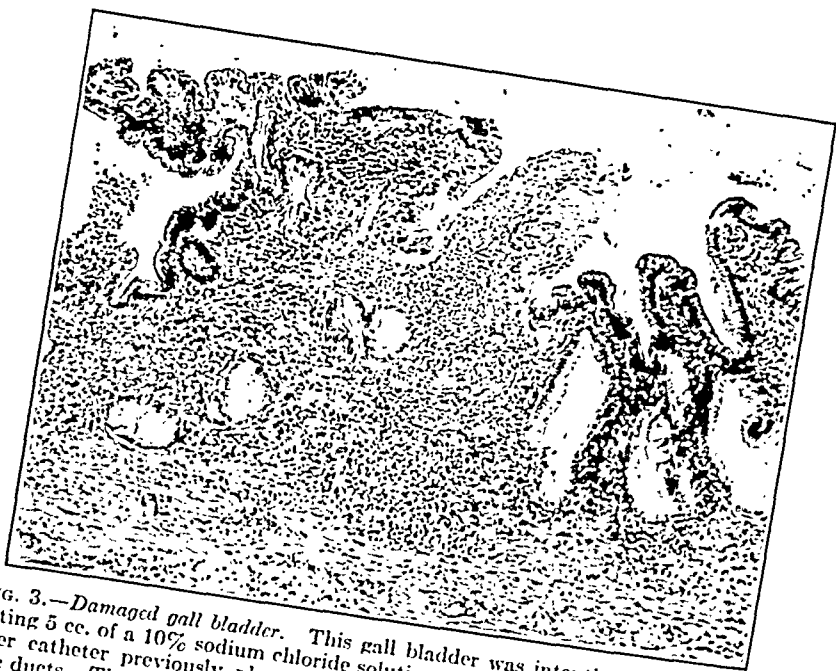


FIG. 3.—*Damaged gall bladder.* This gall bladder was intentionally damaged by injecting 5 cc. of a 10% sodium chloride solution on 2 separate days through a small rubber catheter previously placed in the gall bladder through the common and cystic ducts. The damage was evident both grossly and microscopically.

dog, by needle puncture, the cystic duct having been ligated. The dog was killed under an anesthetic in 24 hours and the contents of the gall bladder analyzed for iodine. If one were successful in avoiding the cystic blood vessels and lymphatics, the gall bladder would appear quite normal and be partly empty due to the absorption of some of its contents. The latter was, of course, more noticeable when hepatic bile was used than when gall bladder bile was used. In Table 1 are given the data from these experiments. Analysis showed that from 83 to 106% of the injected iodine was recovered from the gall bladder after 24 hours. It was not always possible to ligate the cystic duct alone. When lymphatics were included in the ligature, slight edema of the gall bladder wall was found. The mucous membrane, however, appeared normal microscopically. Such was the case in the last half of the experiments in Table 1.

TABLE 1.—ABSORPTION OF SODIUM TETRAIODOPHENOLPHTHALEIN FROM THE NORMAL GALL BLADDER.

Dog No.	Iodine as excreted by the liver, placed in the gall bladder, gm.	Iodine recovered from gall bladder after 24 hours, gm.	Percentage of iodine recovered.	Gall bladder.
61	0.139	0.119	85.9	Normal
78099	.097	97.0	"
7230278	.0257	92.0	"
7250278	.0295	106.0	"
7980966	.0901	94.0	"
7990157	.0137	87.7	"
157142	.140	98.0	" *
159142	.145	101.0	" *
180139	.115	83.0	" *
443051	.0462	90.0	" *
445102	.089	87.0	" *
5030645	.0646	100.0	" *

* Lymphatic vessels included in ligation of cystic duct causing slight edema of the gall bladder wall. Mucous membrane is microscopically normal.

Absorption from the Damaged Gall Bladder. This was accomplished by several different methods. As stated, the method used by Johnston⁵ resulted in moderate damage to the wall of the gall bladder. The results from 5 dogs, when this method was used, showed a recovery of from 31 to 62% of the injected iodine after 24 hours (Table 2, Part A). These findings are in agreement with those of Johnston.⁵

Another series of experimental dogs was prepared by introducing a small rubber catheter into the gall bladder through the junction of the cystic and common duct, or through the common duct and thence by way of the cystic duct into the gall bladder. The central hepatic duct was ligated above the entrance of the cystic duct.⁷ A gall bladder prepared in this manner will absorb its full content of physiologic saline solution when left overnight. If accessory ducts had been overlooked, bile was found in the gall bladder and the animal was discarded. The gall bladder mucosa was then damaged

TABLE 2.—ABSORPTION OF SODIUM TETRAIODOPHENOLPHTHALEIN FROM THE DAMAGED GALL BLADDER.

Dog No.	Iodine placed in gall bladder, gm.	Iodine recovered from gall bladder after 24 hours, gm.	Percentage of iodine recovered.	Gall bladder damage.
<i>Part A—Cystic Duct Ligated, Dye Dissolved in Bile Injected into the Gall Bladder by Needle Puncture.</i>				
39	0.0485	0.0153	31	Severe
38046	.0244	53	Moderate
568140	.0878	62	"
790047	.0279	52	"
956049	.0259	52	"
<i>Part B—Catheter in Gall Bladder by Cystic Duct. Damaged by 10% Saline. Dye Dissolved in Bile, Placed in Gall Bladder.</i>				
266	0.144	0.0361	25	Moderate
2961438	.039	27	"
347138	.080	57	"
911138	.0558	40	"
948138	.056	41	"
93141	.0499	35	Severe
122146	.0317	21	"
1701407	.0189	13	"
327141	.0303	21	"
<i>Part C—Catheter in Gall Bladder by Cystic Duct. Damaged by 10% Saline. Bile, from Dog Previously Given Dye Intravenously, Placed in Gall Bladder.</i>				
253	0.156	0.1073	68	Slight
254156	.0524	33	Moderate
408079	.0467	59	Slight
410079	.0292	37	Moderate
<i>Part D—Necrotic Gall Bladder Produced by Ligating Blood Supply. Bile from Dog Previously Given Dye Intravenously, Injected into Gall Bladder.</i>				
409	0.0515	0.0088	17	Necrotic
454016	.0018	29	"
471054	.0031	5.8	"

by injecting 5 cc. of a 10% sodium chloride solution daily for 2 or 3 days. At the end of this time, the gall bladder was found to pour out 10 to 30 cc. of turbid fluid daily. A known quantity of sodium tetraiodophenolphthalein in bile was placed in such a damaged gall bladder and the contents analyzed 24 hours later. From 13 to 57% of the injected iodine was recovered (Table 2, Part B). Gall bladder or hepatic bile obtained from a dog previously given sodium tetraiodophenolphthalein intravenously was also placed in the damaged gall bladder (Table 2, Part C). The dog at the conclusion of a single experiment was always sacrificed in order to ascertain that there was no leakage around the catheter. Grossly, the gall bladders of this group showed varying degrees of damage. In general, the more severe the histologic evidence of damage the greater the absorption of the iodine salt.

An effort was then made to produce a gangrenous gall bladder by ligating the cystic vessels so as to determine the fate of sodium tetraiodophenolphthalein under these conditions. This was done by using bile secured from a dog previously given the dye intra-

venously. From 5.8 to 29% of the injected iodine was recovered after 24 hours (Table 2, Part D): The gall bladders were necrotic, but there was no recognizable leak.

*Method of Iodine Analysis.** The iodine in the bile was determined by a hydrolytic reduction method (a modification of the method by Chiray, Lesage and Taschner¹ followed by subsequent oxidation and titration with thiosulphate. Briefly, the procedure was as follows: The sample withdrawn from the gall bladder was diluted with water to a definite volume. To an aliquot of this, containing 0.5 to 2 mg. I, NaOH and Zn powder were added and the mixture heated for approximately $\frac{1}{2}$ hour. After neutralizing and filtering, H_2SO_4 is added, then Br, followed by phenol, after which potassium iodide is added and the iodine titrated with thiosulphate. Control determinations on the dye gave an average value of 50% I \pm 2% in the dye, and this figure was used in calculating subsequent results. Determinations on known amounts of dye and varying quantities of bile, and also on varying dilutions of a solution of the dye in bile, gave satisfactory recoveries.

Comment. The question can be raised as to whether one is justified in regarding a gall bladder as normal when the cystic duct and a needle puncture hole have been ligated. The gall bladder, which we have designated normal, absorbed fluid and concentrated bile and appeared to be normal both grossly and microscopically (Fig. 1). In view of the marked difference in the absorption of sodium tetraiodophenolphthalein in the normal gall bladders and those which were damaged, we feel justified in regarding them as physiologically normal.

The damaged gall bladders used in these experiments may be compared to the gall bladders of acute and subacute cholecystitis as seen in man. They could hardly be said to simulate chronic cholecystitis. -

The experiments on gangrenous gall bladders here reported probably have no clinical significance, since the gangrenous gall bladder in the human practically always has an obstructed cystic duct.

Summary. 1. A method has been devised to compare the absorption of sodium tetraiodophenolphthalein from the normal and damaged gall bladder of the dog.

2. From 83 to 106% of the dye was recovered from the normal gall bladder after 24 hours.

3. From 5.8 to 68% of the dye was recovered from the damaged gall bladder after 24 hours. The variation depended at least in part upon the degree of damage.

Conclusions. 1. Sodium tetraiodophenolphthalein is absorbed more rapidly from the damaged than from the normal gall bladder of the dog.

2. It is reasonable to suppose, therefore, that this factor may play some part in the failure to make the diseased gall bladder visible in clinical cholecystography.

* We are indebted to Dr. P. A. Bott and Dr. R. D. Cool of the Department of Pharmacology, University of Pennsylvania, who suggested this method.

3. Sodium tetraiodophenolphthalein is not excreted by the liver in the bile in the same form as it is given intravenously.

4. The data obtained regarding the rate of absorption of sodium tetraiodophenolphthalein by the normal gall bladder, further strengthen Johnston's⁵ contention that the rapid changes occurring in clinical cholecystography must be explained upon the basis of expulsion of the dye through the cystic duct rather than absorption of the dye by the gall bladder.

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A STUDY OF THE OSSEOUS REMAINS OF THE "MOUND BUILDERS" OF EASTERN ARKANSAS.*

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A RACE of people who were sedentary agriculturists and hunters once lived along the Mississippi River and its tributaries. They erected earthen mounds of varying sizes and for this reason they have been generally referred to as the "Mound Builders." The period of their occupation of the Mississippi Valley is not definitely known. The exact relation of the "Mound Builders" to the American Indian of colonial times has not been established and it is questionable as to whether European explorers of the 16th century had any contact with them. So far as is known, the only contact the "Mound Builders" of Eastern Arkansas may have had with Europeans was with the men of DeSoto in 1539 to 1543. The explorers who visited the western bank of the Mississippi River after DeSoto and before colonization of this area, which is now the eastern part of Arkansas, were usually definite in their statements that the people they saw in this region were few in number and probably remnants of tribes.³

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The accounts of these early explorers are important since they indicate that between the time of DeSoto's visit and the beginning of trade and colonization along the Mississippi and Arkansas Rivers, this area was not densely populated. The population was never great enough to support the large burial grounds which have been found in Mississippi and Crittenden Counties in Eastern Arkansas. These burial grounds, therefore, were probably made in precolonial times, that is, prior to the 17th century.

The object of this study was to determine whether examination of the bones of the "Mound Builders" would reveal lesions which are comparable to those that are recognized as fairly definite clinical entities at the present time. The skeletal material obtained from more than 400 graves was examined and the diseased skeletons were retained for further study and roentgenologic investigation of their structure. In this communication, only representative material which was well preserved will be presented. In order that the maximum of details of structure could be obtained by roentgenologic examination, repeated examinations with varying exposures were made.

The osteologic material which we have studied came from the edges and the immediate vicinity of typical mounds built by the "Mound Builders" in Crittenden and Mississippi Counties in the eastern part of Arkansas. It is definitely known that the present-day inhabitants of this area have never buried their dead near these mounds. The osseous remains were obtained from shallow graves which averaged about 18 to 24 inches in depth. In some graves there was evidence that the body had been inclosed in bark which formed a sort of coffin. For burial, the bodies were usually extended and placed on their backs. The heads were not pointed in any definite direction, say toward the West which is so definitely characteristic of burials by our present-day races. In addition to the osseous remains, the caches contained pottery, stone weapons and implements, beads, and other characteristic possessions. Not a single European trade object was found in any of the caches, refuse pits, or in the vicinity of the graves. The absence of these trade objects lends further support to the fact that these burials were made in precolonial times.

Anomalies. There were evidences of certain congenital anomalies. One femur of a young adult showed the characteristic difference in appearance of the proximal end which is seen in congenital dislocation of the hip joint. The dislocation in this case had occurred on the right side. The humeri of a young adult were of different sizes. The left humerus was 4 cm. longer than the right and appeared to be the normal of the two. The differences in size and length were probably the result of a poliomyelitis, a birth injury, or a congenital anomaly. There were examples of spina bifida of the lumbar and sacral vertebrae. There was one "steeple head" or oxycephalic

skull. Several skulls had been deformed by cradling or splinting during infancy.

Questionable Blood Dyscrasias. Two skulls had prominent parietal bosses which were heavy and thick (Fig. 1). The entire dome of each of these skulls had the appearance of coral. This appearance had resulted from the peeling away of the thinned, outer plate. The inner surfaces of these skulls were normal. The distal ends of the femurs of one of these skeletons were increased in diameter; the tibiae had round, smooth anterior surfaces and were slightly increased in diameter (Fig. 2). Femurs and tibiae of other skeletons revealed similar changes.

The foregoing lesions of the skull and long bones may be present in certain hemolytic anemias, and in sickle-cell anemia. The congenital hemolytic and erythroblastic anemias usually affect the children of races with dark skins. The recognition of the roentgenologic appearance of the changes in the craniums and long bones, which may be associated with certain blood dyscrasias, is a recent addition to our diagnostic procedures. Cooley, Witwer, and Lee,² in 1927, reported 7 cases of splenomegaly in which unusual changes occurred in the bones. All of the patients were children. Five of these cases had been previously reported in 1925. Baty, Blackfan, and Diamond,¹ in a study of erythroblastic anemia, added 20 cases to those already reported. In this latter study one finds a most detailed description of the roentgenologic changes occurring in the long bones in these hemolytic anemias. In 1924, according to Moore,⁴ Graham reported the finding of changes in the long bones in a case of sickle-cell anemia, but there were no cranial alterations. However, since Graham's report, it has been a common observation that in sickle-cell anemia there may be alterations both in the long bones and in the cranium. Whipple and Bradford⁶ do not believe that the pathologic changes observed in certain of these anemias are adaptive reactions to hyperplasia of marrow. They suggested that the abnormalities may be attributable in part to some metabolic disturbance on the order of abnormalities of bone in cases of scurvy or acromegaly. They concluded that all the abnormalities of these blood dyscrasias may be related to some racial or inherited defect. These remarks serve to illustrate that there are several groups of anemias which may produce skeletal and cranial changes.

In both sickle-cell and hemolytic anemia, the cranial vault may reveal an increased porosity of the cancellous portion of the bone. In the severe and later stage of the disease there may be thickening of the diploë to several times the normal. The outer table is thin and, during life, is not easily seen in the roentgenogram. In the dried specimen, the outer table may crumble away; such skulls may be described as possessing "increased porosity." The roentgenogram reveals the increased thickness and numerous fine stria-

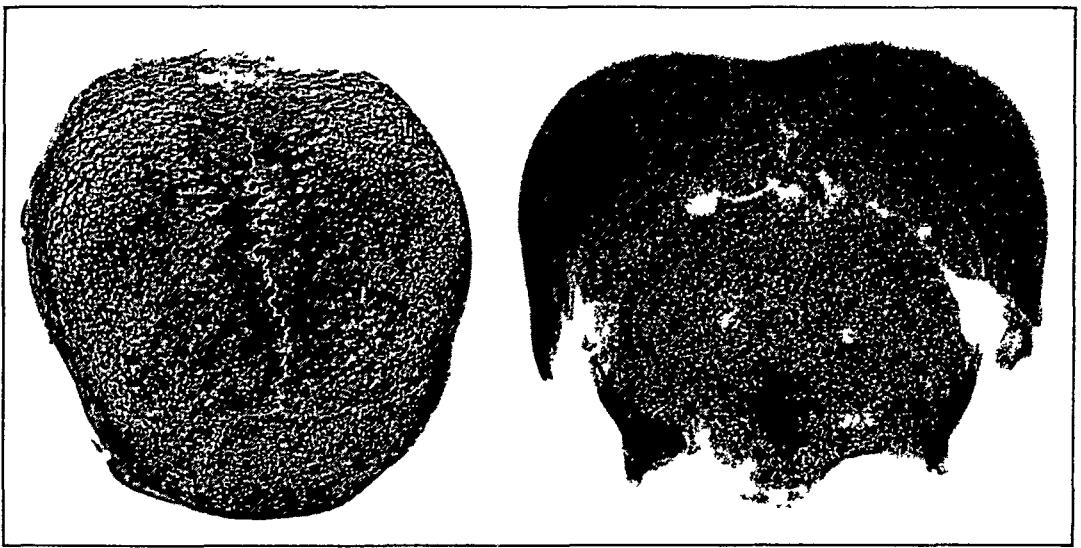


FIG. 1.—Gross and roentgenologic changes characteristic of certain anemias



FIG. 3.—Skull, tibiae, ulnae, fibula and radii showing gross and roentgenologic changes characteristic of syphilis.

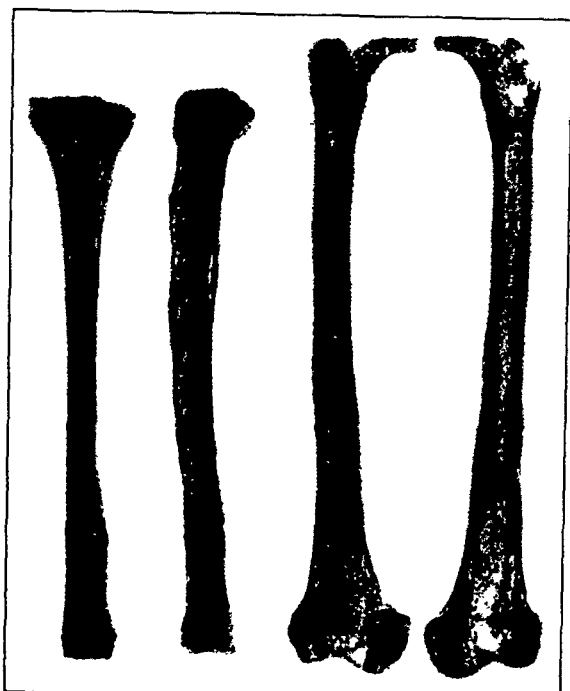


FIG. 2.—Long bones showing changes characteristic of certain anemias.

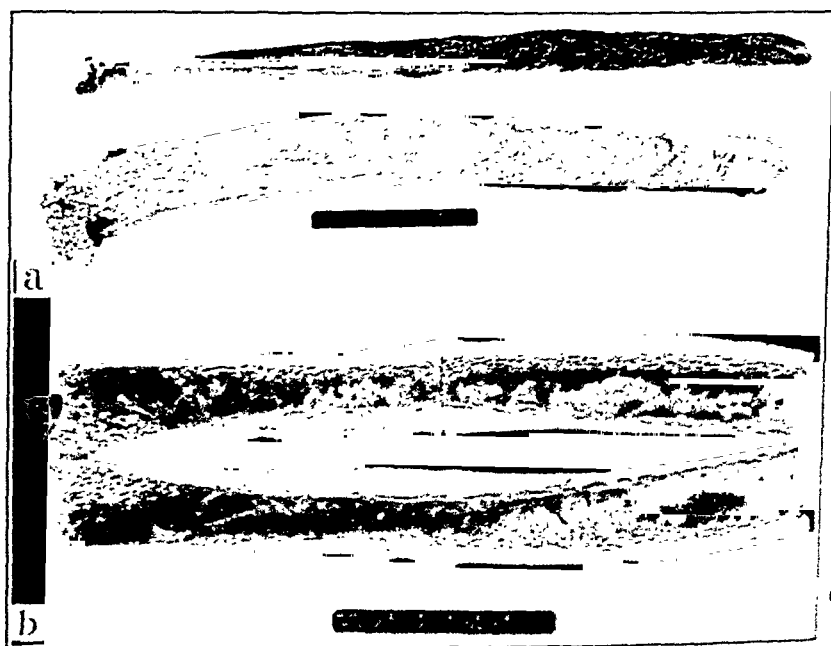


FIG. 4.—a, Tibia and fibula before sectioning; b, tibia after section; this bone shows irregular cortical thickening—so-called "blistering syphilis."

tions, so-called sun-bursts, which run perpendicularly to the tables of the skull. The long bones are wide because of an increase in the medullary portion. Rarefaction of the medullary portion results in a transparent appearance of the roentgenogram. There may be irregular trabeculations in the pelvis, vertebræ, ribs, clavicles and scapulæ.

It is a singular fact that these prehistoric American people should have had changes in their skulls and long bones, which are so suggestive of blood dyscrasias, such as erythroblastic, hemolytic, sickle-cell and other anemias. To those who have an interest in racial susceptibility and immunity to certain diseases, the presence of anemias which are peculiar to the Mediterranean races and Africans among "Mound Builders" tends to support the suggestion of Whipple and Bradford, namely, that these anemias are the result of some racial or inherited defect. That the "Mound Builders" may have had these anemias serves as further evidence that this race had a dark skin which is characteristic too of the American Indian. The morbidity of these blood dyscrasias among the "Mound Builders" will never be known, but it was not great. It probably was no greater than is the incidence of sickle-cell anemia among their colored "brethren," who at the present time tread the soil above their remains. Osseous changes, which are comparable to those described in this study, have been reported to have occurred among ancient Egyptians and ancient French people of the Gallo-Roman Period.⁷ Moore made similar observations regarding ancient Peruvians.

Syphilis. There were lesions of the long bones, clavicles, skulls, and bones of the nose, which were similar to those of syphilis; the tibiæ often showed changes in the shafts. These changes, which were most prominent over the anterior surface of the middle third of the tibia were fusiform or oval in shape and shaded off rapidly toward the lower third, which was covered with muscle during life. Some tibiæ were greatly altered in appearance; the sharp anterior crest was replaced by a rounded surface and this thickening gave the shaft the appearance of having been bowed anteriorly. Fibulæ, radii, ulnæ, and clavicles showed similar changes, that is, a deforming osteitis and a low-grade osteomyelitis of varying degree.

In Table 1 we have tabulated the different bones of the same skeleton which showed lesions which may be characteristic of

TABLE 1.—THE NUMBER OF BONES WHICH REVEALED CHANGES CHARACTERISTIC OF SYPHILIS.

Skeleton	Tibiæ	Fibulæ	Radii	Ulnæ	Humeri	Crania
1	2	1				
2	1	..	1	1		
3	2	1	
4	2	2	2			
5	1	..	1			
6	2	1	2	2	..	1

syphilis. There were other isolated specimens which showed similar changes, but since no other part of the skeleton was thus affected they have not been enumerated.

The best evidence of osseous syphilis would be to find changes characteristic of this disease present in the tibiae, fibulae, radii, ulnae, and cranium of one skeleton. Such changes were found in one skeleton (Fig. 3) and are enumerated (Skeleton 6) in Table 1. Aside from this skeleton, we discovered other tibiae, fibulae, clavicles, which were the site of lesions suggesting lues, particularly gummata. In one skull the nasal bones as well as the bones of the roof of the mouth were eroded. In this case, in which the changes in the bones of the nose and hard palate were characteristic of syphilis, we have a fragmentary history. In the grave were deposited trinkets similar to those usually buried with children, and in no other grave of an adult was this custom observed. This suggests that possibly this person had the mentality of a child.

Syphilis of the skull may manifest itself in different ways; each lesion may produce a characteristic appearance and the signs of the various lesions may be present in the same skull. The gross appearance of a dried syphilitic skull therefore depends on the degree of the various predominating lesions. If periostitis with thickening was the predominating lesion, the skull would be increased in weight. The outer and inner surfaces of the calvarium may show various changes. Numerous abnormal vascular grooves and foramina indicate an increased blood supply, which is characteristic of early stages of syphilis of bone. The outer surface may present bony elevations which have a more or less convex surface, the so-called "tuberculated" form of syphilitic osteitis. Other syphilitic lesions of the cranium in most cases are localized, although extensive regions may be involved as a result of confluent foci. The skull of Skeleton 6 of Table 1 is an example of the "tuberculated" form of syphilitic osteitis.

The gross and the roentgenologic appearances of the foregoing specimens are in agreement that the changes were similar to those produced by syphilis. However, the possibility that these changes were artefacts, the result of the long time that the skeletons had remained in the ground, was considered. To obviate any such mistake, some of the specimens were sectioned. A tibia (from Skeleton 4, Table 1) was sectioned and photographed (Fig. 4). Further description of this specimen is not necessary, for it is rather characteristic of the so-called "blistering type" of syphilis of bone. More detailed sectioning of these bones for microscopic study was attempted but could not be done. Complete disintegration resulted from attempts at decalcification.

Syphilitic involvement of the bones of the body which are superficially situated is a chronic inflammatory process. The diagnosis of syphilis which is made solely on data obtained from the study of

skeletal material is always open to question, because there is no certain way of proving that the changes present were not the result of a chronic inflammatory process similar to that which may follow typhoid fever.

Operative Procedures. One skull, which may have been an example of trephining by means of a stone implement, was most interesting. This skull belonged to a normally developed adult man. It revealed an irregularity of the external surface of the left frontal bone, which involved only the external plate. In the upper part of the left parietal bone were 3 irregularly outlined perforations. The edges of these perforations were smooth and showed evidences of healing. There were no bordering areas of necrosis or evidences of fractures in this skull. The bone adjacent to these perforations was not thickened nor did it reveal any abnormal alterations. There was a healed fracture of the left clavicle of this skeleton.

The procedure of boring holes in the skull was practised extensively by certain races of ancient South Americans. They used flints shaped for boring or scraping to perform these operations. The motive for such a drastic procedure is not known. Authors with a kindly and humane feeling toward primitive people who practiced trephining have seen in it a surgical procedure, that is, a genuine desire to relieve suffering. Primitive people had highly developed instincts of self preservation. It would be difficult to imagine that a primitive person would submit to such a procedure after observing the terrific mortality which must have accompanied these "operations." Fractures which have been observed in other bones of the same skeletons might well be evidence that these unfortunate persons did not voluntarily submit to the "operation."

We are, however, fully aware of the fact that trephining was seldom, if ever, practised by the aborigines north of Mexico; therefore, this skull is presented as a probable example of this procedure. If it is not an example of trephining, the perforations in this skull probably were the result of some other traumatic agent which was followed by infection, erosion of the bones, and attempts to heal. There were many examples of the scraping of long bones. These operations were usually done on diseased bones and will be discussed in detail in another communication on this subject. The "Mound Builders" extracted teeth and reduced fractures.

Miscellaneous Lesions. A tibia, which belonged to a young adult, had an osteoma at the distal end. This tumor was of the congenital type. No lesions that seemed to fulfill the requirements of malignant growths were observed in any specimen.

Two healed fractures were found; one of these involved the right humerus and the other involved the left tibia. The fragments had healed in perfect alignment. There were two tibiae which showed localized destruction of their cortices in the proximal thirds. These lesions were thought to be the result of puncture wounds, such as

might be inflicted by an arrow, or which might be the result of a Brodie's abscess. In each case a rather marked osteitis had been present in the region around the site of bone destruction for a long time.

The teeth that were still present were generally sound. There were a few perfect sets of teeth; however, positive statements concerning the dentures of this race cannot be made because so many of the teeth had fallen out after death. A decayed tooth does not withstand being buried for a long time and it does not withstand trauma incident to exhuming, or the subsequent drying. There were mandibles which showed evidence of marked dental infection and suppuration. Owing to the scarcity of stone, the corn was ground in wooden utensils; the meal, therefore, contained a minimal amount of grit to wear down and to destroy their teeth.

Hypertrophic changes about the borders of the lumbar vertebrae were occasionally observed. Hypertrophic changes were present about the knee joints in two skeletons. Three thoracic vertebrae were fused and bowed anteriorly in the very characteristic manner of spondylitis deformans. Fusion of the axis with the atlas was found in one skeleton.

There were no examples of an infectious type of arthritis or osseous tuberculosis. The presence of a lesion characteristic of tuberculosis would not be expected in bones which had been buried for so long a time. There were several examples of a severe, destructive osteomyelitis. One femur was of special interest since it was enlarged to twice its normal diameter and it was literally honey-combed in appearance, with numerous intracommunicating canals throughout its entire length.

Comment and Summary. As a rule, the skeletal remains of these people were well formed and well proportioned, which indicated that they had an excellent muscular system. Anterior bowing or lateral deformities of the bones of the legs, such as are seen in rickets, were not found. Irregular epiphyseal lines were not seen in any of the roentgenograms. The legs were straight, the pelvis were narrow, and the arms were of moderate length. The heads were well formed if they had not been subjected to certain self-inflicted deforming procedures during their growth. In such cases the antero-posterior diameters were decreased and the bregmatic and lateral diameters were increased; these changes produced "flat heads." In some of these deformed heads there were symmetrical depressions above the orbits. One can be certain that the shape of these heads was not the result of disease but the result of cradling or moulding during growth.

Examples of the so-called "infectious arthritis" were not found. Hypertrophic changes about the margins of the knee joints and vertebrae were occasionally present. There were no changes characteristic of tuberculosis. An excellent example of spondylitis

deformans was present in three thoracic vertebrae. Osteomyelitis in extreme degrees was present in several specimens. The teeth were usually good. Healed tooth sockets indicated the antemortem extraction of teeth. Cauterizing or scraping of diseased long bones of the legs was a fairly common procedure. Fractures of long bones were set with a fair degree of precision.

The gross and roentgenologic presence of bony changes which may be seen in certain anemias were observed in the bones of the long extinct "Mound Builders" of Eastern Arkansas. One can be reasonably sure that when these lesions are present in the cranium and when they are accompanied by changes in the long bones that the individual had a blood dyscrasia. The diagnosis of syphilis among precolonial Americans who lived in Eastern Arkansas cannot be made absolutely. It is our opinion that sufficient evidence is present to say they had it. It is important to emphasize that the tibiae and other long bones which were studied and described in this report were well preserved. We are entirely in accord with the findings of Williams⁸ and of Means,³ namely, that syphilis was endemic in North America before known contacts with Europeans. However, the findings recorded here are not presented as evidence of either the new or old world origin of syphilis.

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EXPERIMENTAL RADIUM POISONING.*

II. CHANGES IN THE TEETH OF RABBITS PRODUCED BY ORAL ADMINISTRATION OF RADIUM SULPHATE.

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In 1924, Theodore Blum,¹ a dentist, who was treating a painter of luminous watch dials for necrosis and osteomyelitis of the jaw bones, suggested that radium was the cause of this condition. This observation led to the investigations which established radium poisoning as an industrial hazard. In spite of the fact that it has

* This investigation has been made with the assistance of a grant from the Committee on Therapeutic Research, Council on Pharmacology and Chemistry, American Medical Association.

since been shown² that gingivitis, buccal infection, necrosis and osteomyelitis of the jaw are among the first symptoms to appear, no histologic studies of the teeth in the human cases or in experimental radium poisoning have been reported. Since the teeth are embedded in alveolar bone, which characteristically shows marked damage as a result of its radium content, and since they are similar to bone in composition, it would appear unlikely that the teeth and their supporting tissues could escape injury. The teeth are being bombarded constantly by emanations from the radium stored in the bony structures surrounding them and also, as will be shown, by radium actually deposited in the teeth structures.

The changes in the lymph nodes and bone marrow of rabbits who were given radium sulphate *per os* have been described in a previous communication.⁴ These animals not only developed pathologic changes and a general symptomatology closely resembling that of radium poisoning as manifested in the human cases, but also showed marked pathologic disturbances in the teeth. The following report deals with a description of the changes in the teeth and their supporting tissues as noted in this series of rabbits.

To appreciate the pathologic processes discussed in this paper it might be helpful to review briefly the essential features of normal dentition in the rabbit.

The rabbit has 2 pairs of upper incisors. The large anterior upper incisors, which are much curved, show a well marked groove on their labial surface which extends from the apex to the cutting edge. This longitudinal groove gives the appearance of a channel whose walls slope acutely to meet in a sharp angle. Behind each of these teeth is a diminutive posterior incisor. The single pair of lower incisors are chisel-shaped and their roots extend far back into the jaws and also show the curve characteristic of an advanced rodent dentition. The cheek teeth, of which there are 12 maxillary and 10 mandibular, are all molariform. The columns of teeth are pressed together so that the anteroposterior diameter of each tooth is much less than the transverse. The lower molar teeth present on their occlusal surfaces three sharp grooves. These molar teeth articulate in such a manner that every lower tooth opposes 2 upper teeth; the first and last teeth of the upper jaw, however, have each only 1 opposing tooth. The incisors, as well as the cheek teeth, grow from persistent pulps and are therefore never shed. The rate of growth of the incisor teeth is from 2 to 3 mm. per week throughout the life of the animal (Orban³), but the growth of new dentine is balanced by a constant wearing down process (attrition), so that the teeth remain at a constant length. The investment of enamel in the incisor teeth, instead of being continued around the whole circumference of the tooth, is confined to the anterior and lateral surfaces, on the former of which it is thickest; the posterior surface is covered by a layer of primary cementum. The enamel organ, however, completely surrounds the apex of the roots.

Histologically, the dentine forms the greater portion of the entire tooth. Two layers of dentine can be distinguished, one of which is a wide layer showing a more or less rhythmic and uniform stratification, with occasional shallow undulations. This is the layer which borders the pulp cavity. An outer, narrower layer consists of granules which gradually increase in size as they approach the periphery, where they coalesce into quite large "globules of calcification." As the dentine is followed towards the root the inner, stratified layer gradually decreases in width until it finally disappears, while the outer, granular layer, which is here considerably coarser, tapers to the apex.*

Material and Method. Four rabbits 6 months of age were used, of which 2 were males, each weighing 2700 gm. and 2 females, each weighing 1800 gm. The animals were kept on a normal and adequate standard diet throughout the experiment. Each animal was fed several drops of a suspension of radium sulphate in glycerin by medicine dropper 3 times daily for a period of 90 consecutive days. By the end of this period, each rabbit had received orally about 100 micrograms of radium sulphate. Glycerin was found to be a suitable vehicle and the animals seemed to enjoy the sweet taste, thus insuring ingestion of most of the radium salts. The rabbits were observed daily for physical changes, and blood studies were made biweekly. The animals survived for 3, 12, 13 and 18 months, respectively, after the cessation of radium administration.

Gross Changes of Teeth. For the first 2 months of the radium administration the teeth showed no abnormal changes. During the third months, however, the lower incisor teeth of all showed a brown mottling. In the next few weeks the mottling became more marked and similar discolorations gradually appeared on the other teeth. The entire length of the extraalveolar portion of the incisor teeth showed, on the labial and lateral aspects, a transverse corrugation which was characterized by ridges, unevenly spaced and varying in thickness and height. The longitudinal groove on the labial surface of the upper incisor became shallower and more rounded. At this time, and associated with these dental changes, there was a gingivitis, and in manipulating the jaws there was manifested a progressive tenderness. Soon after the cessation of radium administration, a gradual abrasion of the lower incisor teeth became evident and this continued, until, in the animal which survived the longest (18 months) the lower incisors became worn down to the gum margin. The upper incisors showed to a lesser degree the same changes, the sharp incisive edges being worn off (abraded) with the formation of broad occluding surfaces.

The upper and lower molar teeth also showed striking gross changes. They were irregularly abraded, some being worn down to the gum margin. Some presented a single, flattened, oblique sur-

* For a more detailed description of the histology of rabbits' teeth the reader is referred to the article by Orban.*

face, while others were sharp, ragged and irregular. Small, oval and rounded pits were found on the lateral surfaces of the teeth. Irregular masses of bone had grown in between the teeth (Fig. 2) and produced a solid junction (ankylosis).

In the meantime, the animals developed abscesses of the jaw, and Roentgen ray examination revealed irregular areas of rarefaction of the mandibular plates. When representative teeth were placed on extremely rapid, dry, photographic plates (Standard Orthonon, 4.5 by 6 cm.) for 6 days, definite shadows (autophotographs) corresponding to the shape of the various teeth were produced, indicating the presence of radium within the tooth. Normal rabbit teeth treated in the same manner produced no changes on the photographic plates (Fig. 3).

Histologic Changes. Striking abnormalities were found in all structures of the teeth, in the periodontium and in the adjacent bone (Fig. 1A). (Compare with Fig. 1B.) The dentine showed evidence of disturbed calcification. In place of the normal, rhythmic stratification of the dentine, one found an irregularity in the spacing of the calcified and uncalcified layers. These incremental lines were sometimes localized in fan-shaped areas (Fig. 4) without any definite relationship to the pulp cavity. Not only was there disturbance of the normal architecture, but there was also an excessive deposition of calcium in many of the incremental lines. The globules of calcification were very large and their union was incomplete, resulting in an increase in the number and size of the interglobular spaces. There were also irregular zones of uncalcified or poorly calcified matrix, which frequently presented a porous or cystic appearance. Thus, zones of very poorly calcified or completely uncalcified dentine were found irregularly distributed, or alternating with areas of excessive calcification, and without any definite relationship to the pulp cavity. Certain areas in the dentine revealed a decreased number of irregular tubules, which were widely spaced.

The intraalveolar portions of the teeth were irregular serrated as a result of deeply excavated areas of resorption of dentine, which were frequently filled by a proliferating fibroblastic tissue extending from the periodontium. Similar spaces, filled with the same type of proliferating fibroblastic tissue, were found in the center of the dentine structure, giving the appearance of internal areas of resorption. Serial sections showed that the so-called internal areas of resorption communicated with the excavated areas on the surface of the tooth. These excavated areas were frequently lined by a deposition of cementum. The cementum in places was of the primary variety, consisting of a fine fibrillar structure, whereas in other places it was of the secondary variety, consisting of cells embedded in a matrix and resembling bone. In certain areas, especially around the roots, the secondary cementum showed a multilaminated

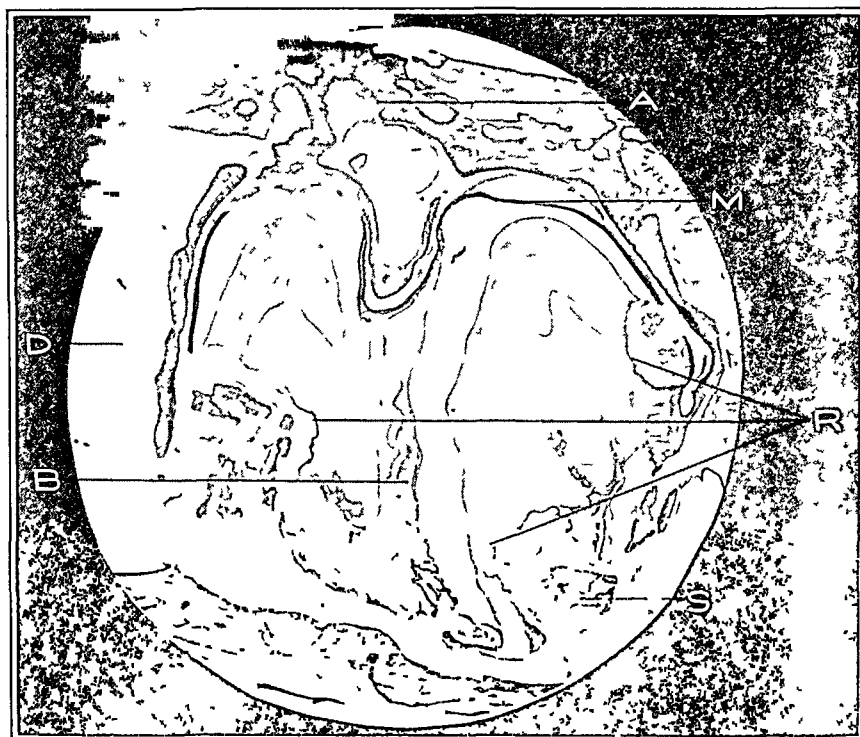


FIG. 1A.—A cross section of molar tooth showing deeply excavated areas of resorption of dentine (R), filled with proliferating fibroblastic tissue and small spicules of newly formed bone (S). Resorption of alveolar bone (A). Heavy deposition of cementum (M). Resorption of intradental bony septum with fibroblastic tissue replacement (B). Acellular alveolar bone marrow (D).

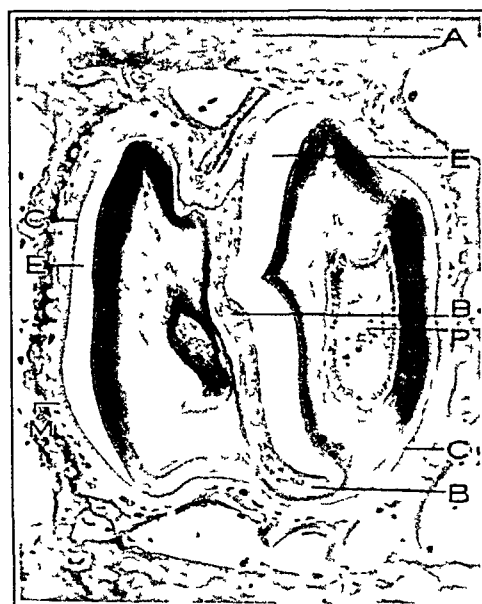


FIG. 1B.—Cross section of lower molar tooth of normal rabbit (after Orban) alveolar bone (A). Enamel space (E). Intradental bony septum (B). Pulp (P). Cementum (C). Periodontal membrane (M).

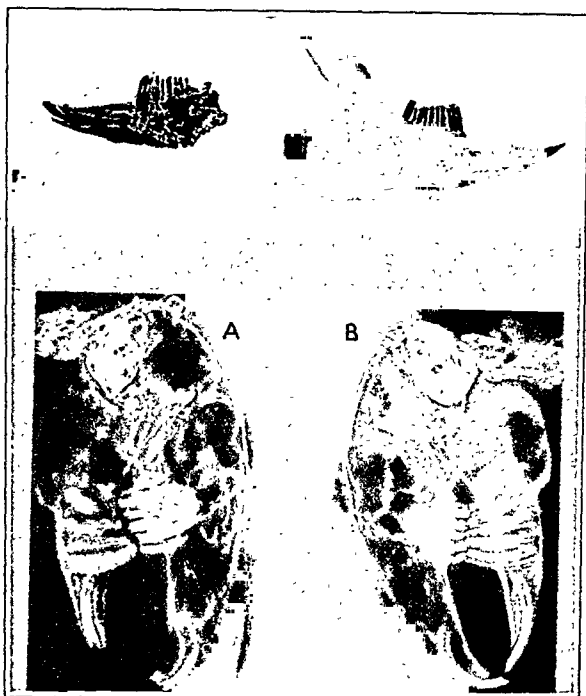


FIG. 2.—Upper.—Ingrowth of bone between molar teeth, and abrasion of the incisor tooth. Due to its fragility, caused by the osteoporosis, the mandibular plate was separated in the process of preparation. Note the appearance of the normal mandible at the right.

FIG. 2.—Lower.—Note the striking changes in the molar and incisor teeth of the radium-fed rabbit (A) as compared with the normal control rabbit (B).

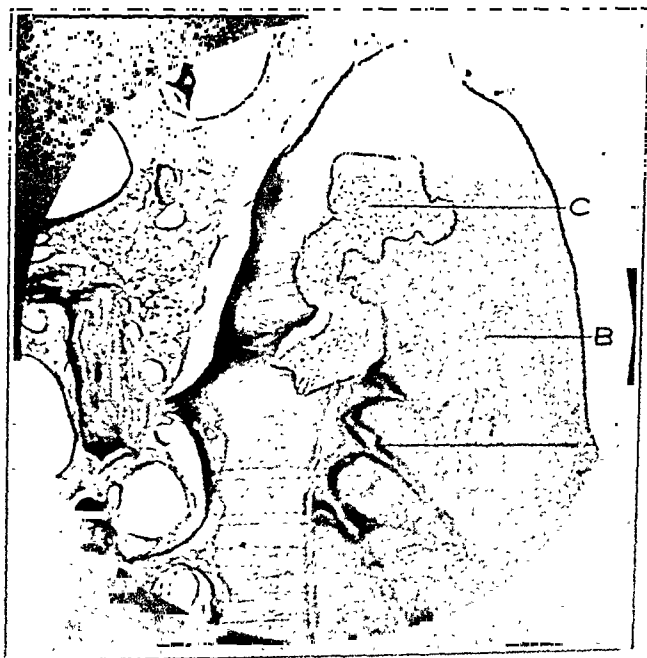


FIG. 4.—Incremental lines (A) localized in fan-shaped areas and large globules (B) of calcification of dentine. Internal area of resorption (C).

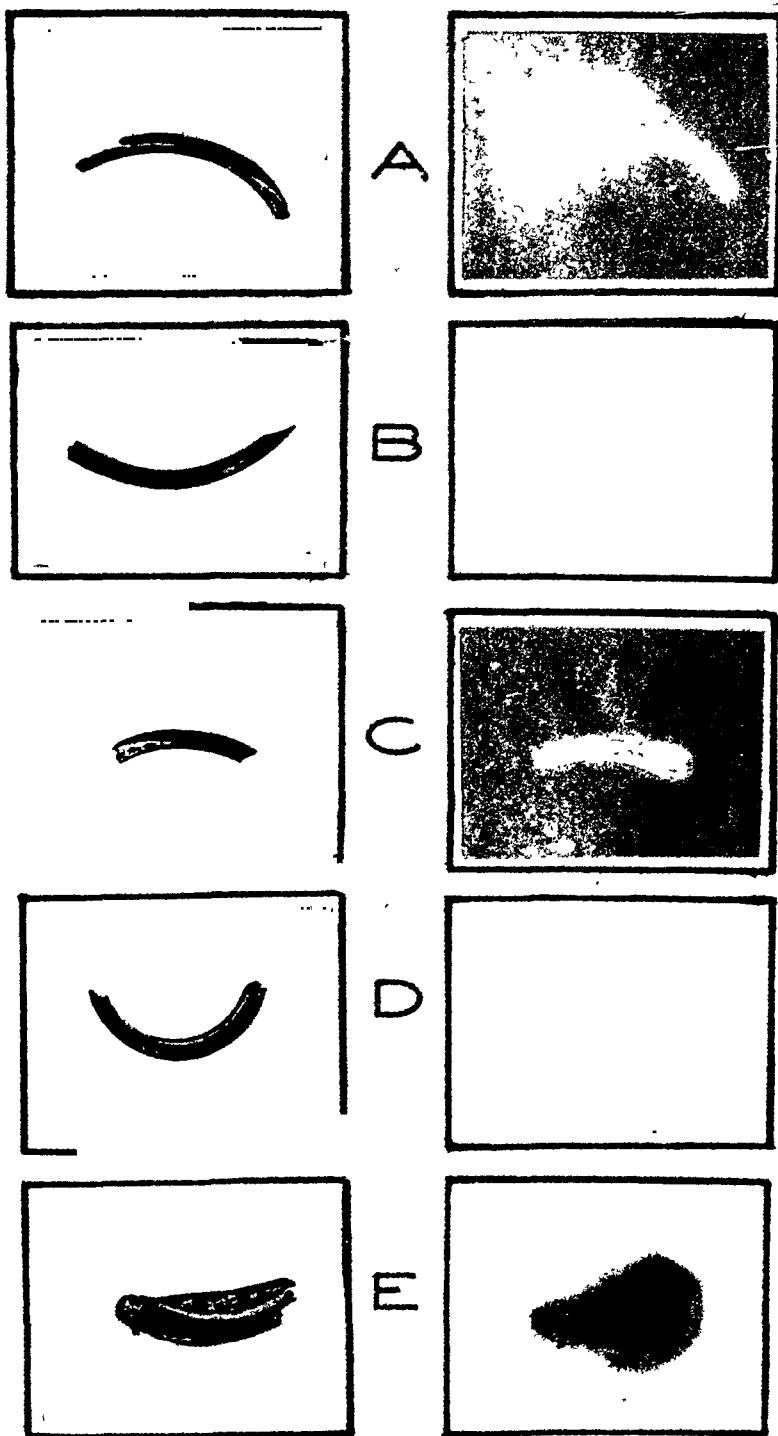


FIG. 3.—Photographs and corresponding autophotographs of teeth of radium-treated rabbits. Teeth B and D were from normal (control) animals and produced no autophotographic shadows.



FIG. 5.—A large spicule of dentine (A) containing large globules of calcification, surrounded by fibroblastic proliferation (B). Surface of resorbed tooth lined by hyperplastic layer of secondary cementum (C). Small epithelial-lined cyst in periodontal membrane.

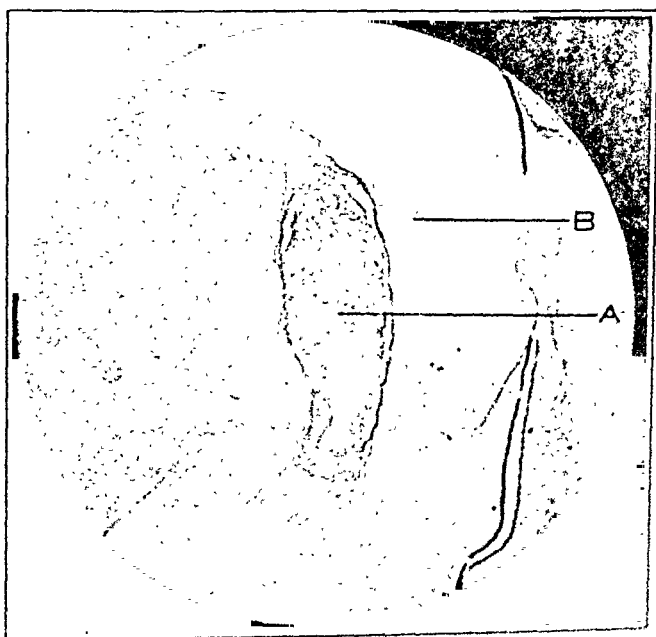


FIG. 7.—Pulp chamber filled with secondary dentine (A) and separated from the primary dentine (B) by a zone of darker staining undifferentiated dentine.



FIG. 6.—Large mass of newly formed bone (A) forming a solid junction with the tooth. Note the external and internal areas of resorption (B).

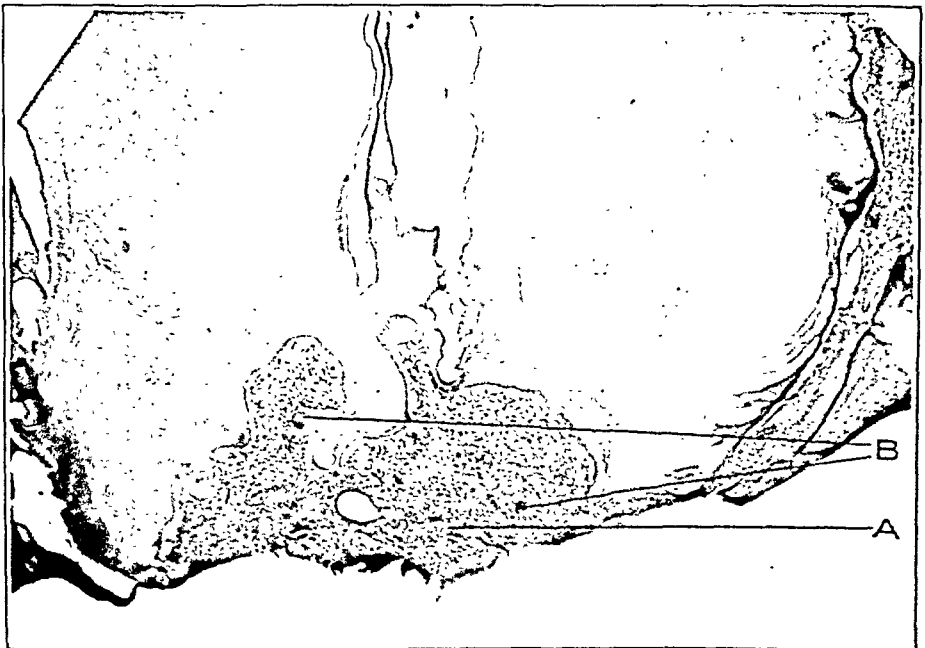


FIG. 8.—Extensive proliferation of atypical epithelial cells (A) about the apex of a molar tooth. Note the globular, calcified masses (B).



FIG. 9.—An epithelial lined cyst containing cholesterol crystal spaces (A) in the periodontal membrane.



FIG. 10.—Hypertrophy of the interdental papillae (A) (hypertrophic gingivitis) adjacent to an area of resorption (B).

structure indicating a marked hyperplasia. The cementum cells in the superficial layers appeared normal, but in the deeper layers near the dentine the cells had completely degenerated and the lacunæ were empty. At times, a layer of primary cementum was found to alternate with a layer of secondary cementum; in other instances, fragments of fractured dentine were found to be reunited by an ingrowth of excessively calcified cementum. The fibroblasts of the peridental membrane showed extensive proliferation. The cells were arranged in irregular, coursing bands and the nuclei showed numerous mitotic figures. In places, this tissue was infiltrated by a few lymphocytes and plasma cells. It showed but slight vascularity and contained no giant cells. It showed also occasional, globular, calcified bodies with concentric laminations (cementicles). As stated above, this hyperplastic tissue not only invaded the tooth structure but also extended into the marrow spaces of the surrounding bone. The bone of the alveolar processes had been extensively replaced by large, irregular masses of newly formed bony trabeculæ and presented a compact structure wherein the lacunæ were closely set and the marrow spaces smaller than in the corresponding sections from control animals. Large, irregularly shaped masses of this uniform bone were frequently found attached to the teeth by secondary cementum, producing solid junctions (ankylosis) between bone and the resorbing teeth (Fig. 6). In some sections almost the entire intraalveolar portions of the teeth were found to be resorbed and replaced by newly formed bone, which was also focally united to tooth structures. It was observed that the dentine bordering the pulp cavity showed no areas of resorption. This observation is similar to that of J. Tomes on the resorption of deciduous teeth.⁵

Fractures of the dentine involving the calcified areas were occasionally encountered. Irregular spicules of dentine, varying in size and showing large globules of calcification, were found completely separated from the tooth and surrounded by proliferated fibroblastic tissue (Fig. 5). Osteoclasts were not found along the borders of the resorbing dentine nor in the vicinity of the sequestered pieces of dentine; in fact, only a few of these cells were found near the resorbing alveolar bone. The bone marrow of the alveolar processes was almost completely acellular and presented a myxomatous appearance. The arterioles, in many places, showed varying degrees of intimal proliferation; occasionally, they even presented complete obliteration of the lumen. The media showed degenerative changes and small areas of necrosis.

No normal pulp tissue was found in any of the sections. The pulp chambers were completely or partially filled with secondary dentine which showed a scant number of irregular dentinal tubules. Between this irregular secondary dentine and the surrounding layer of primary dentine there was a transitional zone consisting of

darker staining, more compact, undifferentiated dentine (Fig. 7). Only rarely were any cellular elements found in the pulp chamber and these usually consisted of fibroblasts and occasional blood-vessels. Where secondary cementum was found in the pulp chambers it was located near the roots, apparently representing an ingrowth from without.

Frequently the enamel organ showed various stages of degeneration, including complete necrosis. The ameloblasts, normally present as a single layer of tall, regularly arranged columnar cells with basally placed nuclei, showed various degrees of flattening; in some areas they appeared as low cuboidal cells with centrally placed nuclei, while in other areas there was marked atrophy or complete disappearance of this layer. The epithelial cells of the stratum intermedium showed hyperplastic changes, as evidenced by the widening of this layer and the presence of more numerous mitotic figures than are normally seen. The cells of the stellate reticulum showed necrosis as evidenced by the fading of their nuclei and the loss of their cellular outlines. About the apices there was an extensive proliferation of atypical epithelial cells. These cells, at times, bore a resemblance to those of the stratum intermedium and were arranged in streaming strands or in concentric whorls. Intermixed with these cells were cells resembling those of the stellate reticulum, the latter being in various stages of degeneration (Fig. 8). In some instances there were small, isolated, irregularly shaped areas of necrosis, in which the cellular details were completely lost and vacuolization was pronounced. Occasionally, globular, calcified masses, presenting a concentrically laminated appearance, were found in this hyperplastic tissue. Although the above description strongly suggests that these areas arose from the enamel organ, it is also possible that they had their origin in the epithelial rests normally present in the periodontal membrane.

A conspicuous feature of many of the sections was the presence of cysts, obviously arising in the periodontal membrane. These structures were lined by a broad layer of stratified squamous epithelium and contained desquamated epithelial cells, albuminous fluid, and cholesterol crystal spaces. The manner of their development was suggested by the finding of areas of necrosis and small cystic spaces in the center of rounded masses of proliferated epithelial cells, which probably had their origin in the aforementioned epithelial rests of the periodontal membrane. The abscesses of the jaws found during life were considered to have arisen through infection of certain of these radicular cysts (Fig. 9).

The gingival tissue also showed proliferative and degenerative changes. Not infrequently, small nodular protrusions, originating from the interdental papillae, were seen. These were most frequently found near or protruding into excavated portions of the

teeth. They were covered by a layer of hornified, hyperplastic, epithelial cells and the subepithelial tissue was fibrous and poorly vascularized. In histologic appearance, they resembled papillomas (hypertrophic gingivitis) (Fig. 10).

Summary. Observations on animals given radium sulphate *per os* show that the radium is stored not only in the alveolar bone of the jaw but also in the teeth themselves, producing a pronounced alteration of the entire morphologic picture of the tooth.

There is a marked disturbance in calcification, with resorption of teeth and the formation of ankylosis by the ingrowth of newly formed bone, which also replaces the absorbed bone of the alveolar process. The essential changes in the enamel organ consist of flattening and atrophy of the ameloblasts, with hyperplasia of the stratum intermedium and subsequent degeneration and necrosis of the entire formative structure. The normal pulp tissue is replaced by abnormal, irregular secondary dentine masses. The surrounding periodontium shows an extreme hyperplasia of fibroblastic tissue, with invasion of surrounding structures. The development of cysts arising from epithelial rests in this membrane is also an interesting finding.

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THE GASTRIC ACIDITY IN ALCOHOL ADDICTS.

WITH OBSERVATIONS ON THE RELATION OF THE B VITAMINS TO ACHLORHYDRIA.

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ALCOHOL is an agent alleged to impair gastric secretion. As early as 1880 Fenwick⁶ stated that the prolonged excessive use of alcohol caused injury to the gastric mucosa with subsequent lack of secretion. Some 25 years later Faber and Lange,⁵ on the basis of pathologic studies, stressed alcohol as an exogenous cause of "gastritis" and the accompanying anacidity. As recently as 1926 Faber⁴

again emphasized this view. Merritt and Moore¹⁴ in 1930 reported the gastric analyses as normal in 7 of 8 alcohol addicts. Minot, Strauss and Cobb¹⁵ studied by fractional analysis the gastric secretion of 43 patients with "alcoholic" polyneuritis, using either the Ewald or the alcohol test meal, but administering histamine to only half of their subjects showing achlorhydria. By these methods they found the incidence of achlorhydria to be 50%, hypochlorhydria 33% and adequate free acidity 17%. The expected normal incidence of achlorhydria in their subjects was 12%. As they were unable to find significant statistical data concerning the state of the gastric secretion in alcohol addiction, these authors could not conclude whether the increased incidence of achlorhydria and hypochlorhydria was characteristic of "alcoholic" polyneuritis or merely of chronic alcoholism.

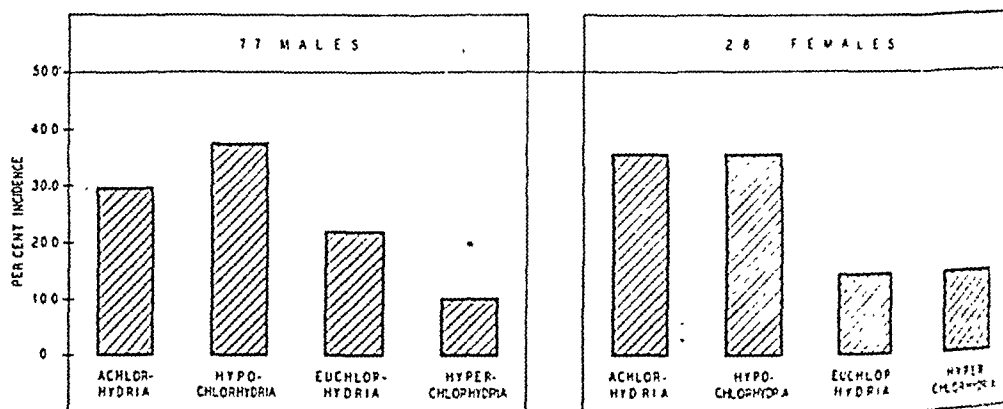


FIG. 1.—Distribution of types of acid secretion in 105 alcohol addicts.

In order to obtain significant data concerning the state of the gastric acidity in chronic alcoholism, we have studied the gastric acidity curves of 105 alcohol addicts, of whom 77 were males and 28 were females. These subjects used alcohol in large quantities over periods ranging from months to years, either daily or periodically. The method of conducting the test was that advocated by Bloomfield and Pollard.² The alcohol test meal was used, and histamine given if free acid was absent in the first three samples. The gastric analyses reported in this paper were obtained as a rule between the third and seventh day of hospitalization.

The criteria established by Vanzant and associates¹⁹ are used to classify these subjects into four groups according to the maximum degree of free acid found. Achlorhydria is the complete absence of free acid after the administration of histamine. Hypochlorhydria includes free acid values from 1 to 20 units in males and 1 to 19 units in females. Euchlorhydria, or normal values, ranges from 31 to 59 units of free acid in males and 20 to 49 units in females. Hyper-

chlorhydria includes free acid values of over 59 units in males and of over 49 units in females.

Liver function studies were conducted on these patients by methods reported in a previous study on catarrhal jaundice.¹⁰ Since the degree of bromsulphalein retention¹⁶ at the end of 30 minutes seemed in general to parallel the degree of liver dysfunction as measured by the other tests, we are reporting in this paper only the results of this test. A complete hematologic status was determined at weekly intervals on each of these patients. Haden's⁸ methods and criteria, corrected for our laboratory, were used on patients examined prior to September, 1935. Since then Wintrobe's²¹ methods and criteria have been used.

RESULTS. The distribution of the types of acid secretion obtained in our 105 patients is presented in Figure 1. Adequate secretion (euchlorhydria and hyperchlorhydria) of free acid occurred in 32% of the 77 male subjects and in 29% of the 28 female subjects. Inadequate secretion (achlorhydria and hypochlorhydria) of free acid was found in 68% of the male subjects and in 71% of the female subjects. Achlorhydria occurred in 30% of the males and 35% of the females, while hypochlorhydria was found in an additional 38% of the males and 36% of the females. In Table 1 we have

TABLE 1.—AGE AND SEX DISTRIBUTION OF ACHLORHYDRIA IN 105 ALCOHOL ADDICTS.

Ages	Males				Females			
	Total cases	Anacidity			Total cases	Anacidity.		
		Total cases	Per cent frequency	Per cent normal expected frequency		Total cases	Per cent frequency	Per cent normal expected frequency
20-29	2	0	0	2.90	5	0	0	4.70
30-39	20	8	40.0	3.50	8	1	12.5	7.50
40-49	30	8	26.6	10.00	9	5	55.5	19.10
50-59	21	6	28.5	13.90	4	3	75.0	18.00
60-69	4	1	25.0	31.70	2	1	50.0	21.90
Totals	77	23	29.9	10.28	28	10	35.7	13.25

tabulated the incidence of achlorhydria in our subjects according to age and sex, and in Figure 2 we have compared these findings with the expected frequency in a group of normal individuals from the data of Bloomfield and Pollard.² In each age group in both male and female subjects between the ages of 30 and 59 the frequency of achlorhydria exceeded the expected normal incidence. In the male groups between 30 and 59 years of age there are sufficient cases for the results to be significant. In the female groups the number of cases is small, but since the results parallel the findings in the male groups they, too, are probably significant.

Pellagra was present in 27 (26%) of our subjects, all but 5 of whom had in addition a polyneuritis. Adequate secretion of free acid occurred in 11%, hypochlorhydria in 37%, and achlorhydria in 52% of the subjects in this group. The incidence of achlorhydria in this group is about the median of that reported by various workers⁹ in endemic pellagra.

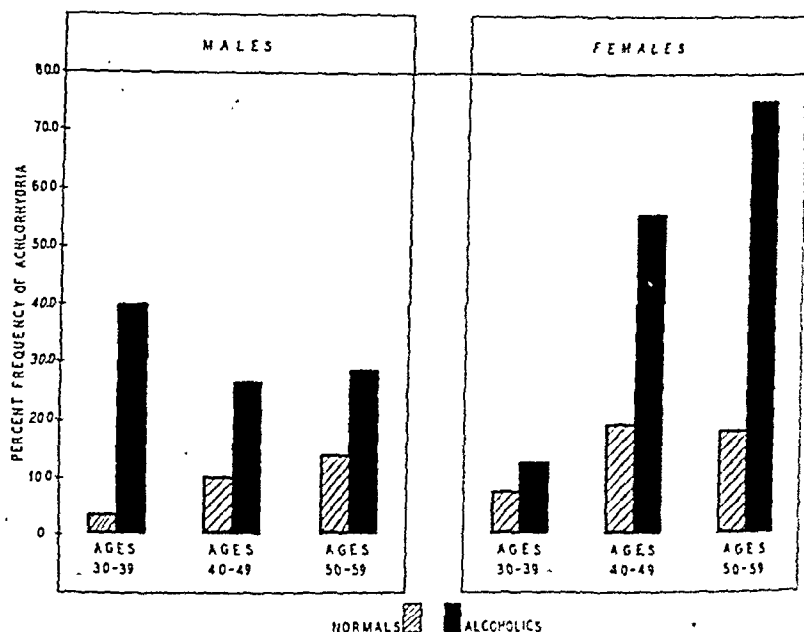


FIG. 2.—Age and sex distribution of achlorhydria in alcohol addicts and normal subjects.

Polyneuritis was present in 74 (70%) of our subjects, 22 of whom also had pellagra. Since the gastric acidity of the pellagrins has been noted separately, we have included in this group only the 52 subjects without pellagra. Adequate secretion of free acid occurred in 29%, hypochlorhydria in 42%, and achlorhydria in 29% of the subjects in this group. Our incidence of achlorhydria in this polyneuritic group without pellagra is smaller than the 50% reported by Minot, Strauss and Cobb.¹² This difference can be largely explained by the facts that they used histamine to stimulate gastric secretion in only one-half of their cases showing achlorhydria, and that 14 subjects having pellagra were included in their polyneuritic group.

Our 26 subjects who did not have pellagra or polyneuritis are included in an "uncomplicated" group. Adequate secretion of free acid occurred in 58%, hypochlorhydria in 27% and achlorhydria in 15% of these subjects. The expected frequency of achlorhydria in a group of normal subjects of the same age and sex distribution

would be about 12%. The difference of 3% is probably not significant. In this group of 26 "uncomplicated" alcohol addicts, 16 gave reliable histories from which the VIT/CAL ratios^{3b} could be estimated, which permitted us¹¹ to estimate quantitatively the adequacy of their diets in respect to vitamin B. These subjects, as pointed out by Jolliffe, Colbert and Joffe,¹¹ failed to develop polyneuritis either because their vitamin B intake was adequate or because of the short duration of the deficiency. In this group of 16 subjects without clinical evidence of vitamin B deficiency, only 1 subject had achlorhydria, 1 had hypochlorhydria, and the remaining 14 yielded adequate acid values. This result is no different than one would expect in a group of normal subjects of the same age and sex distribution.

Quantitative anemia occurred in 80% of our 105 subjects. The red cells of all subjects, however, are classified as normocytic, microcytic, or macrocytic as determined by the volume index or the mean corpuscular volume. Normocytosis was present in 36%, microcytosis in 26% and macrocytosis in 36% of the subjects. Achlorhydria occurred in 40% of the normocytic group, in 38% of the microcytic group and in only 20% of the macrocytic group. In the subjects having achlorhydria, normocytosis occurred in 45%, microcytosis in 31% and macrocytosis in only 24%.

Correlation of the liver function tests with the gastric acidity is especially important in view of the high incidence of achlorhydria in liver disease. As a group those deficient in acid secretion showed a slightly greater impairment of liver function, as measured by the tests used, than did those with adequate acid secretion. In the acid deficient group the average of the initial bromsulphalein retention was 28.5 ± 12.6 as compared with 21.5 ± 12.7 in the acid adequate group. In view of this large probable error in each group the difference is not statistically significant. Because of the marked difference in incidence of achlorhydria in the pellagrins, the polyneuritics, and in the "uncomplicated" group, we have compared the degree of liver dysfunction in these three groups, irrespective of the state of the gastric acidity. The average initial bromsulphalein retention in the pellagrins was 37.5 ± 14.9 , in the polyneuritics 24.1 ± 12.1 , and in the "uncomplicated" group 22.1 ± 11.3 . The results in the polyneuritic and "uncomplicated" groups are practically identical. In view of the size of the probable error, the greater retention of bromsulphalein in the pellagrins over that of the other two groups is probably not significant. These results may represent only the inadequacy of our methods of testing the functions of the liver.

Discussion. The study of the gastric acidity in this group of 105 alcohol addicts during the latter half of the first week of hospitalization showed achlorhydria in about one-third of all subjects, with another one-third showing hypochlorhydria and one-third show-

ing adequate secretion of free acid. The expected frequency of achlorhydria in a normal group of the same age and sex distribution as calculated from the data of Bloomfield and Pollard² would be about 11%. The frequency of achlorhydria in this group of alcohol addicts is, therefore, about 3 times the expected normal. Is this high incidence of achlorhydria due to the direct effect of alcohol *per se*? Is it due to or merely associated with the dietary deficiency causing polyneuritis or pellagra? Is it due to or associated with the macrocytic anemia or the liver disease? We have shown that there is no evidence relating it to macrocytic anemia or liver disease in our subjects. We believe that it is not due to alcohol *per se*; that it is associated with polyneuritis but is not due to vitamin B deficiency; also, that it is associated with pellagra but not definitely due to a lack of the pellagra preventive factor.

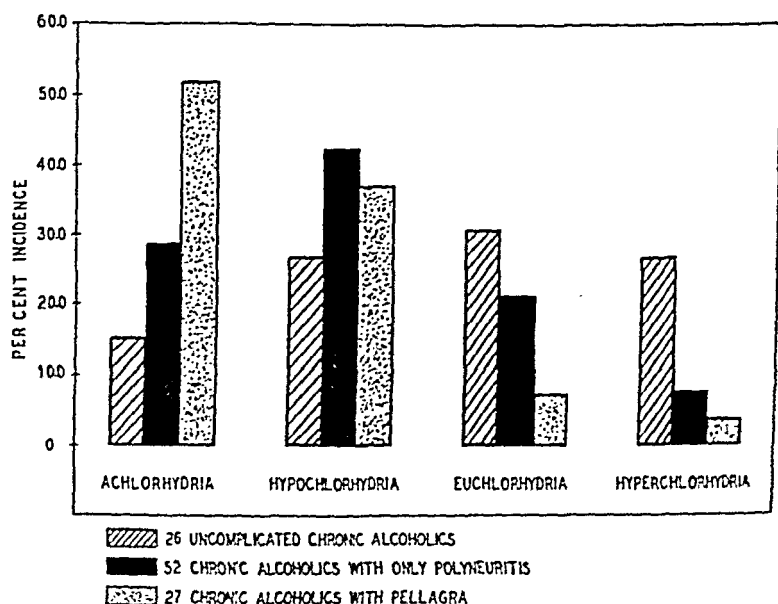


FIG. 3.—Incidence of types of gastric secretion in uncomplicated chronic alcoholics and in those having polyneuritis or pellagra.

In support of these contentions we present the following evidence. Achlorhydria occurred in 52% of the pellagrins, in 29% of the polyneuritics, and in 15% of the "uncomplicated" group (Fig. 3). The duration of the immediate bout of alcoholism in the above three groups, though there are exceptions, can be roughly estimated as follows: months to years in the pellagrins, weeks to months in the polyneuritics, and days to weeks in the "uncomplicated" group. The incidence of achlorhydria, therefore, seems to vary directly with the duration of the alcoholism. Evidence, however, that this assumption is not valid is furnished by a critical analysis of our data. It is true that the entire "uncomplicated" group had

an average *per diem* intake of alcohol less than the average of the polyneuritic group. Nevertheless, many of these subjects drank a sufficient quantity of whiskey over an effective period of time to cause achlorhydria if alcohol *per se* were its cause. To illustrate this point, 9 of the 16 "uncomplicated" subjects giving adequate histories¹⁴ used from 8 to 24 ounces of whiskey daily for periods varying from 6 months to 40 years. The average maximum free acidity in this group was 40 units, with histamine stimulation required in but 1 subject. In the 24 subjects with polyneuritis who gave adequate histories,¹⁴ 11 subjects used 8 to 24 ounces of whiskey daily for periods varying from 6 months to 25 years. The average maximum free acidity in this group was 25 units, but histamine stimulation was required in 8 subjects. Prior to the administration of histamine the free acidity averaged only 7 units. The relative necessity of administering histamine in these two groups indicates the relative incidence of anacidity without stimulation by this drug, and suggests that the difference of maximum free acidity in the two groups is significant. Since the group showing a normal incidence of achlorhydria used as much whiskey and over as long a period of time as the group showing a high incidence of achlorhydria, we believe that alcohol *per se* is not the cause of achlorhydria in the alcohol addict.

The 26 "uncomplicated" subjects did not have polyneuritis because, as shown by Jolliffe, Colbert and Joffe,¹¹ either an adequate intake of vitamin B was maintained or the duration of the deficiency was very brief. Of the 16 subjects in this group whose VIT/CAL ratios could be estimated quantitatively,¹¹ only 1 subject (417) had achlorhydria, 1 (325) showed hypochlorhydria, and the remaining 14 subjects showed adequate acid secretion. In our group of 52 alcohol addicts with polyneuritis we were able to estimate quantitatively the VIT/CAL ratios of 24. As measured by this ratio, each of these 24 subjects had a vitamin B intake below his predicted requirement over a period of time adequate to produce polyneuritis.¹¹ Achlorhydria occurred in 7 of these (Subjects 258, 300, 327, 336, 388, 392 and 468), an incidence of 29%, which is identical with the incidence found in the entire polyneuritic group of 52 subjects. From the fact that achlorhydria is relatively common in alcohol addicts with proven vitamin B deficiency and of but normal frequency in alcohol addicts without vitamin B deficiency, it would appear that vitamin B is an achlorhydria preventive factor. This evidence is, however, not conclusive, as the achlorhydria preventive factor may be a separate entity frequently inadequate in American diets when vitamin B is also inadequate. In support of the conjecture that the achlorhydria preventive factor and vitamin B are not the same fraction of the vitamin B complex we have the work of Kitamura and Shimazono¹³ and Keefer,¹² who show that achlorhydria is not associated with beriberi, the classic clinical picture of vitamin B

deficiency. Additional evidence that vitamin B and the achlorhydria preventive factor are not identical may be inferred from the gastric acidity of the 5 subjects in this study who had pellagra without polyneuritis. Cowgill^{3b} used the presence or absence of polyneuritis as the criterion of the adequacy or inadequacy of a diet in the determination of the vitamin B requirement of man. These 5 subjects, on this basis, were not vitamin B deficient. Achlorhydria, however, was present in 4 of these 5 subjects, while the fifth showed hypochlorhydria. In endemic pellagra achlorhydria occurs in about 35 to 90% of the subjects;⁹ if these pellagrins consumed a diet similar to Goldberger's⁷ or the traditional diet of Southern pellagrins, consisting of salt pork, corn, and molasses, they would presumably have an adequate vitamin B intake.^{3b} In endemic pellagra, therefore, vitamin B in amounts sufficient to prevent the development of polyneuritis does not prevent the development of achlorhydria. This suggests that the achlorhydria preventive factor and the pellagra preventive factor are frequently associated, or they may be the same fraction of the vitamin B complex. But how would a deficiency in the pellagra preventive factor cause achlorhydria in a subject with polyneuritis uncomplicated by clinical pellagra? In our experience the alcohol addict with polyneuritis usually consumes a diet qualitatively inadequate in the entire vitamin B complex as well as in vitamin B. The failure of most subjects to develop pellagra can be attributed to the fact that vitamin B deficiency manifests itself by polyneuritis in from 7 to 21 days of estimated absolute deficiency,¹¹ while clinical evidence of deficiency in the pellagra preventive factor requires a relatively longer period of time to become manifest. If the vitamin B deficiency, that is polyneuritis, does not result in the restriction of alcohol and the resumption of an adequate diet, clinical pellagra may still not develop unless the patient is exposed to a dermatitic exciting factor present in sunlight. It is possible therefore that a lack of the pellagra preventive factor causes achlorhydria even though clinical pellagra may not exist. Cowgill,^{3a} however, was unable to impair gastric secretion in dogs by means of the Goldberger diet. In view of the recent work of Ruffin¹⁷ and Smith and Spies¹⁸ it would be interesting to note the effect of sunlight on the gastric secretion of these animals. Cowgill^{3a} was able, however, to impair gastric secretion by feeding a diet inadequate in the entire vitamin B complex, and to cause a return of gastric secretion by the addition of Vitavose to the diet. From these experiments Cowgill inferred that vitamin B was necessary to maintain adequate gastric secretion. Vitavose, however, contains in addition to vitamin B other fractions of the vitamin B complex, and this conclusion is not necessarily valid. In this connection Webster and Armour¹⁹ show that autoclaved yeast, in which the vitamin B is presumably destroyed, is effective in restoring normal gastric secretion in ani-

mals on a vitamin B complex deficient diet, though not as effective as non-autoclaved yeast. They also note that vitamins A, D or C apparently play no rôle in the maintenance of normal gastric secretion.

From the entire line of reasoning here presented it seems to us that an achlorhydria preventive factor is contained in the vitamin B complex. It is probably not the heat labile antineuritic vitamin B fraction. It is closely associated with the heat stable antidermatic pellagra preventive fraction. In view of the facts that achlorhydria is not constantly associated with pellagra and that vitamin G is now thought to consist of several fractions such as the pellagra preventive factor, the antiblack tongue factor, lacto-flavin, and vitamin B₆,¹ it seems probable that the achlorhydria preventive factor and the pellagra preventive factor are not identical. If this latter conjecture is true, one may speculate that this achlorhydria preventive factor is partially heat labile; that it is present in adequate amounts in the diet of Chinese who develop beriberi, but is frequently inadequate in the diet of alcohol addicts who develop polyneuritis or pellagra. It may be suggested therefore, in order to prevent achlorhydria, that the chronic alcohol addict who will not or cannot resume normal drinking habits should supplement his diet with a rich source of the vitamin B complex.

Summary and Conclusions. We have studied by uniform methods the gastric acidity curves of 105 chronic alcohol addicts. Whereas the expected incidence of achlorhydria in a normal group of the same age and sex distribution would be 11%, in this alcoholic group achlorhydria occurred in 33%. Dividing the subjects into three subgroups as follows: the "uncomplicated" subjects, the polyneuritics and the pellagrins, achlorhydria occurred in 15, 29 and 52%, respectively. Achlorhydria was not related to the degree or duration of the alcohol addiction, and did not occur in greater frequency in subjects having macrocytic anemia or showing the greater degree of liver dysfunction. We have discussed the possibility of an achlorhydria preventive factor being a part of the vitamin B complex but not identical with either the vitamin B or the pellagra preventive fraction. We conclude that:

1. Alcohol *per se* does not cause achlorhydria in the alcohol addict.
2. An achlorhydria preventive factor is probably present in the vitamin B complex.

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ROENTGENOGRAPHIC STUDIES OF THE MUCOUS MEMBRANE OF THE COLON.

III. MUCOSAL DETAIL STUDIES AS AN AID IN THE EARLY RECOGNITION OF CARCINOMA OF THE COLON.

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THE detection of growths in the colon has always been attended by great difficulty and in many instances with great uncertainty. We are all familiar with cases where repeated routine Roentgen ray examinations both by the oral method and by means of the barium enema have failed to furnish adequate information, thereby causing us to overlook the presence of a carcinoma. Such experiences are embarrassing to the physician and unfortunate for the patient. This situation has been so keenly felt both by surgeons and clinicians that it is quite needless to cite supporting statistics.

We have attempted to perfect a method which will lessen this possibility of error. There are two main factors responsible for the difficulties encountered in the Roentgen ray diagnosis of the large intestines. The first is anatomic, due to such causes as spasm, congenital and acquired adhesions, malpositions and redundancy. Over such causes, the roentgenologist has but limited control. The second factor is that of the method itself which is employed to detect such lesions, roentgenographically. It is this factor which can be so improved as to give the necessary aid in diagnosis.

It is our purpose to describe a method of "mucosal detail" study which has been in use rather extensively abroad but which has not received the attention in this country that it deserves. The greater amount of the work in this field has, of course, been done with

respect to the mucosa of the stomach. In this field the pioneer work of Kalkbrenner,⁴ Berg^{1a} and Knothe⁵ deserves mention.

Various methods have been described from time to time to enable the roentgenologist to visualize more clearly lesions of the colon and sigmoid. The early work of Fischer² on the double contrast enema has yielded excellent results in visualizing such lesions as polyps, small adenomas or early fungating neoplasms which might be completely lost to view by the single contrast enema because of the fact that by this latter method the lesion is usually completely surrounded and hidden by the dense opaque column of the barium mixture. Weber⁹ more recently has revived this method particularly in demonstrating polypoid lesions and polyposis of the large intestines. Especially in constricting lesions of the colon is this method of double contrast medium of extreme value. Gershon-Cohen and Shay,³ using the double contrast enema, found that with respect to neoplasms of the large intestines, there is no advantage in using this method where the lesion is moderately or far advanced. In their experience, it was most valuable in detecting early intraluminal neoplastic processes which single contrast does not reveal.

Various manipulations have been advocated as a means of clearing away redundant coils of gut and thus helping in the detection of filling defects. Stewart and Illick⁸ advocated the examination of the colon by the oblique roentgenograms and roentgenoscopy, when only the pelvic colon contains barium. By this means they have been able to overcome defects due to such causes as coils of terminal ileum containing barium, low position of the cecum and redundancy of the sigmoid. By their method the sigmoid, posterior rectum and anal region are clearly outlined.

When it comes to the consideration of very early changes in the mucosa of the large bowel, none of the above methods seem to be adequate enough to demonstrate such changes. Yet it is in these very cases of early neoplastic change and infiltration that the early surgical removal of the lesion holds out the greatest hope for cure. The routine barium clysma employed for the Roentgen ray of the colon causes a moderate distention of the viscus, so that only the edges of the gut are visualized. It is only after a certain amount of emptying of the colon has taken place that the actual details of the mucosal folds are obtained. Such studies have been reported by Berg^{1b} and Maingot, Sarasin and Duclos.⁷ However, use of this method as a routine procedure, to the exclusion of all other methods, is not the intention or purpose of our present report, for the very reason that it requires much time, patience and perfection of technique in order to obtain satisfactory results. The effort is well rewarded when employed in very early infiltrative lesions of the colonic mucous membrane which are attended by the best and most favorable results by surgical removal. It is, therefore, incumbent

upon both the clinician and surgeon to be sufficiently conversant with the possibilities of this method in such early lesions in order to insist upon its more frequent use.

Recently we⁶ reported such mucosal studies as observed in the normal colon. The appearance of the mucosal pattern differs somewhat in the different parts of the colon. Thorough familiarity with this normal appearance is absolutely essential for the detection of abnormalities in this mucosal pattern.

Method of Procedure. The first essential for the proper execution of this method is to have as clean a colon as is possible. To effect this the preparation of the patient begins a day previous to the actual examination, during which time only a light low-residue diet is allowed. In the evening before the examination a dose of milk of magnesia or cascara is given. The following morning two enemas containing about a quart of water with some Castile soap is used at 1-hour intervals. Two to 3 hours after the last enema, the patient is ready for examination. A cup of tea or coffee may be allowed in the morning but nothing else. The barium enema itself consists of about 1 quart of a barium mixture prepared in plain water. No milk or mucilage is to be used in the preparation of this solution as they tend to delay the evacuation of the colon.

The slow administration of the barium enema is then started under proper fluoroscopic control, in order to detect the presence of stenosing lesions immediately. As soon as the tip of the contrast material has reached the hepatic flexure of the colon it is discontinued. The patient is then instructed to turn on his right side. Very often the barium will fill out the cecum without giving more barium. Too much contrast material if administered will not only cause distress but in many cases results in leakage into the small intestine. When this has occurred, the subsequent evacuation of the large bowel upon which the success of this method depends will be seriously hindered and will make proper mucosal study almost impossible. A film is then taken with the patient lying on his abdomen. The patient is then instructed to evacuate as much of the barium enema as possible. Repeated fluoroscopic examination is then made to determine whether the correct amount of barium is present to outline the mucosal wall. Sometimes the period of evacuation may take 30 to 45 minutes. Naturally, no technician can be intrusted with this procedure.

We have selected 3 cases for detailed report and have particularly employed both the routine barium enema and the special technique described above in order to demonstrate effectively how lesions which are ordinarily unobserved with the routine enema and were missed by others on previous examination, were distinctly demonstrable by the method of mucosal detail study.

Case Reports. CASE 1.—A male, aged 55, was first seen in April, 1934, complaining of gaseous distention and a certain amount of gastric distress together with general abdominal discomfort, following meals. He had had these symptoms with increasing severity for the previous 6 months. During this period his appetite had remained fair, although he had lost 5 pounds. He gradually developed signs of general weakness and would tire very easily upon the slightest exertion. Two complete gastro-intestinal Roentgen ray series were done during this time but failed to reveal any lesion. The last one was performed 3 weeks before the patient came under our observation. Examination revealed a moderate secondary anemia.



FIG. 1.—Case 1. The appearance of the colon as outlined by the routine barium enema. No defects are discernible in this plate.



FIG. 2.—Case 1. The appearance of the colon as brought out by the mucosal detail method, showing a defect indicated by arrows, which had been missed by the routine barium enema.

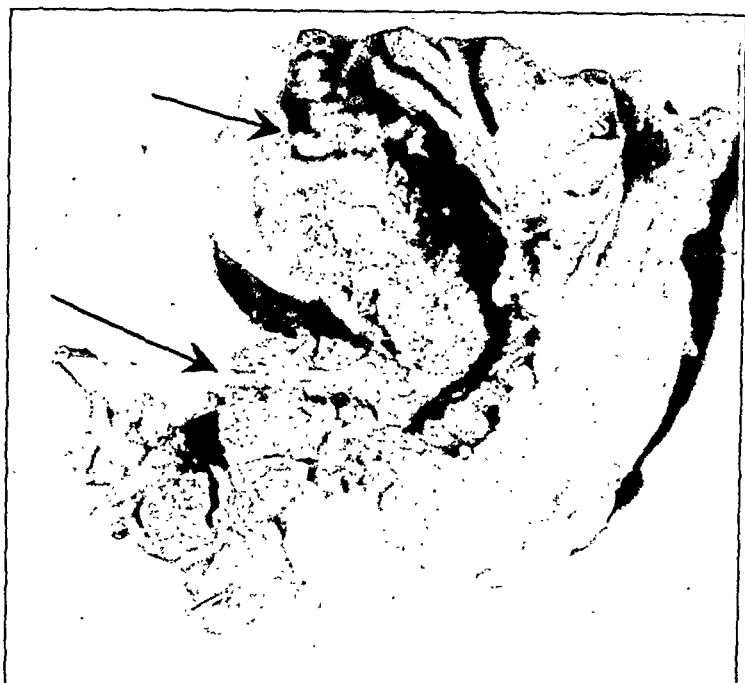


FIG. 3.—Case 1. Specimen of resected colon, showing normal mucous membrane at arrows, with carcinomatous invasion between these points.

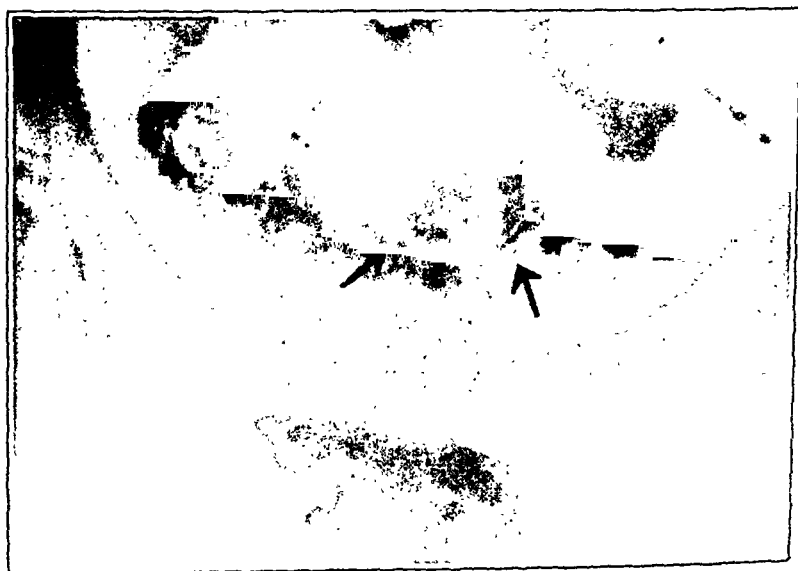


FIG. 4.—Case 2. The outline of the carcinoma as obtained by the mucosal detail method. This was completely obscured by the routine barium enema.



FIG. 5.—Case 3. Appearance of colon after oral administration of barium. No defect discernible.

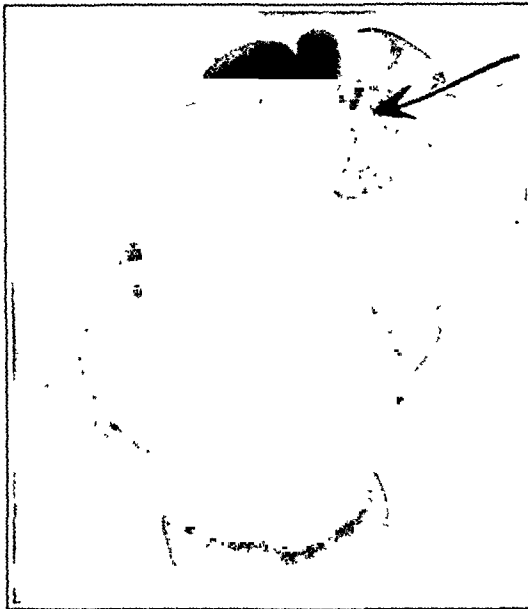


FIG. 6.—Case 3. Appearance of colon after routine barium enema. Obstruction encountered suggestive of colon telescoped into sigmoid, indicated by arrow.



FIG. 7.—Case 3. Appearance of colon by means of mucosal detail method. Carcinoma clearly outlined, located at the head of the intussusception.

The abdomen was distended but no masses could be felt. There was no glandular enlargement present. Rectal examination was negative. The sedimentation rate was 25 mm. in 1 hour.

Roentgen ray examination revealed the following: The barium enema filled the colon without delay (Fig. 1). This failed to show any filling defect that would indicate malignancy. Study of the mucosa by the method just described (Fig. 2) showed a break in the mucosal fold, about 12 cm. from the anus, extending for a distance of about $3\frac{1}{2}$ cm. Proximally to this defect the mucosa was entirely normal. The patient was operated upon and a cancer of the rectosigmoid junction was found and successfully removed (Fig. 3). The patient made an uneventful recovery and a recent follow-up found him in good condition.

CASE 2.—A woman, aged 55, complained of periodic attacks of diarrhea of 6 months' duration. She also had attacks of abdominal pains and gaseous distention. She had lost 5 pounds over 3 months. Careful examination failed to reveal any significant findings, except a positive paratyphoid B culture from the stools. She was treated accordingly for 6 weeks. The abdomen was moderately distended and some tenderness was elicited in the left lower quadrant. No definite tumor mass was palpated. Roentgen ray examination of the colon by means of the routine barium enema showed a complete filling of the colon without any delay. The form and shape of the colon appeared to be normal in this film. No filling defects were noticeable. Examination of the colon, however, by the mucosal method (Fig. 4), revealed a definite defect, $4\frac{1}{2}$ cm. in diameter, in the mid-sigmoid region. Destruction of the mucosal pattern in this area was easily recognized. Operation confirmed the diagnosis of sigmoid cancer which was successfully removed.

CASE 3.—A woman, aged 68, complained of rectal bleeding of 2 weeks' duration. She had a secondary anemia and complained of much weakness and abdominal distress. Roentgen ray examination of the stomach was entirely negative. The barium reached the colon in 24 hours and there was no evidence of any lesion in the colon from this picture (Fig. 5). With the administration of the ordinary barium enema, however, an obstruction was encountered in the middle region of the sigmoid (Fig. 6). The contour of the adjacent sigmoid showed the normal outline. On closer observation, however, one noticed an area of decreased density in the upper portion of the sigmoid which extended for about 6 cm. This finding is very suggestive of invagination of the colon into the sigmoid. The mucosal detail film (Fig. 7) showed a large rounded mass which proved to be a carcinoma which had produced the invagination.

Discussion. Like all laboratory procedures, Roentgen ray examination of the colon is a valuable diagnostic aid, if all possible information can be obtained from it. Too many of us have experienced the embarrassing and unfortunate instance where the existence of a carcinoma of the colon was undetected by the ordinary routine barium clysma. This seems particularly true of small early invading lesions where the surgical results should be at their best. Examination of the films presented in this report shows clearly how it is practically impossible in the majority of cases to make visible such carcinomatous lesions by the ordinary routine barium enema. There are several reasons for this difficulty: (1) With the routine barium enema, there is invariably produced a marked exaggeration in the so-called redundancy of the colon with its consequent over-

lapping of intestinal loops. With the mucosal method this tendency is greatly reduced. (2) With the routine enema, only the edges or borders of the gut are visible and if one is fortunate enough to obtain some irregularity in this outline, the lesion may be detected. With the method which we have described, however, the actual mucosal surface is visible. (3) Various displacements and distortions of the flexures are invariably the result of the complete filling of the colon by the barium or air. (4) The degree of contractility and elasticity of the colon can only be determined by the mucosal method and is completely obscured by the use of the routine barium enema.

In Case 1, for example, the patient had been carefully Roentgen rayed on two previous occasions without any abnormality being detected. Likewise, when the routine barium enema was employed by us, a similar negative result was obtained (Fig. 1). The contrast between this picture and Fig. 2 shows very clearly the comparison of results obtained by the two methods. Had the mucosal method not been done at this time, a third negative report would have been made which would certainly have changed the end result in this case. Likewise Figs. 5, 6 and 7 show the same experience in Case 3.

The repetition of such similar experiences makes us enthusiastic in advocating the use of this method of mucosal study of the colon. We do not wish to convey the impression, however, that it should be used routinely to the exclusion of all other methods. There are cases, for example, as in constricting lesions, where the double contrast medium will give more information than mucosal study alone.

The "mucosal detail" method is described and presented here as offering a means of additional study in a part of the intestinal tract where carcinoma lesions are very often overlooked until they have reached an advanced stage of growth. If used properly in this way, we believe that mucosal detail studies will prove of invaluable help in the early recognition of carcinomatous infiltration of the colon mucosa.

Conclusion. A method is described for obtaining mucosal detail studies of the colon. With the aid of this procedure more information is obtained than when the routine barium enema is employed, and as a result of this, cases of carcinoma of the colon which may be ordinarily missed by the routine barium enema are detected. This method enables detection of the carcinoma at an early stage, when the tumor is still small. The importance of such detection becomes most significant when it is realized that early recognition of the carcinoma offers the only possible hope for cure. Many of the failures of early detection are due to the inadequacy of the usual barium enema. Three cases are described in detail showing the comparative values of the two methods.

This method is not advocated as a routine procedure, but as a diagnostic aid in doubtful cases. The technique requires considerable experience and cannot be intrusted to a technician.

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TUBERCULOUS TRACHEOBRONCHITIS: ITS PATHOGENESIS.

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PULMONARY tuberculosis so overshadows its secondary manifestations that, with the exception of laryngeal involvement, lesions of the mucosa of the respiratory tract have tended to pass unnoticed and unappreciated. During the past 3 years the attention of the staff of the Tuberculosis Unit of the University Hospital has been drawn to a group of patients who have developed dyspnea, a wheezing respiration, cyanosis and intractable coughing in the course of pulmonary tuberculosis. In some instances these signs have appeared when the pulmonary lesion apparently had been retrogressing satisfactorily. Impressively, these patients have done poorly with any type of collapse therapy. In spite of every effort, mortality in this group has been high, 47% of the group showing tracheo-bronchial ulcers or stenoses being dead within a year after the diagnosis had been established.

The clinical manifestations of this complication and the bronchoscopic appearances of the tracheal and bronchial mucosæ are being presented elsewhere by Littig, Barnwell, Culp and Samson.^{1,10} Since the appreciation of the occurrence of these lesions, the diagnosis has been made in 33 cases; of these, bronchoscopy has been

done in 24 cases, while in the rest the clinical signs have been so prominent as to make the diagnosis a practical certainty. In this entire group only 1 patient can be said to have shown any improvement; the others are either already dead or are progressing steadily downward.

Historical. One finds little mention of this complication in recent pathologic literature and the clinical discussions of the complications of pulmonary tuberculosis are usually entirely silent with respect to it. Nevertheless, Eppinger³ was familiar with this type of tuberculosis and in the volume devoted to the larynx and trachea, published in 1880 as volume II of Kleb's *Handbuch der pathologischen Anatomie*, he gave an excellent description of the tracheal lesions occurring occasionally in those dying of pulmonary tuberculosis. In his experience, about one-eighth of the cases without laryngeal lesions showed ulcerative tuberculous tracheitis. He was impressed by the relatively greater frequency of involvement of the lower portion of the trachea. This he attributed to extension from the main bronchi which in turn he considered to have been involved by direct extension from the surrounding lung and caseating bronchial lymph glands. That fibrosing and stenosing tracheal tuberculosis had not been encountered was due, he thought, to the brevity of life consequent upon the establishment of this complication. He remarked upon the tendency for the lesions to be most abundant along the posterior wall.

Although not as cogently discussed as by Eppinger, this condition was mentioned during the previous year (1879) by Heinze.⁷ Nothing of consequence appears to have been added to the subject until 1904 when Hedinger⁴ presented a case which he considered to be primary tuberculosis of the trachea and bronchi. This was in a man, aged 29, with a 3-year history of chronic tracheitis and laryngitis with progressive laryngeal stenosis necessitating tracheotomy, following which he died. Autopsy showed the tracheal wall to be tremendously thickened, with marked reduction of the lumen. The process continued into the bronchi and throughout was characterized by large ulcers. The pulmonary involvement was slight and considered by Hedinger to be bronchogenous.

In the discussion of Hedinger's paper, Hansemann¹ cited an instance of primary tracheal tuberculosis in a man, aged 75, not a single tubercle being found elsewhere than in the trachea.

On the same occasion, Schmorl¹¹ told of 2 cases which he considered primary tracheal tuberculosis, 1 being a youth, aged 18, the other a child of 8 years.

At this time interest in the subject was largely centered in the problem of primary tracheal tuberculosis, an additional case being presented in 1913 by Donagány.² The progressive ulcerative tracheitis described long before was considered of interest only in the autopsy room. The clinical implications of the condition were generally ignored so that when tracheal and bronchial tuberculosis was mentioned at all, the allusion was casual and perfunctory. Kaufmann⁸ and also Hart and Meyer⁵ devoted scant attention to the subject, their treatment being somewhat less complete than that of Eppinger over half a century before.

Recently (1934) Reichle and Frost,² treating of tuberculosis of the major bronchi, have distinguished various mechanisms in the establishment of ulcerative tuberculous bronchitis. Frequently they observed tubercles in conjunction with the submucosal mucous glands and concluded that the infection was carried from the neighboring lung to the bronchial mucosa by way of these glands. For reasons not at all clear, they called this mechanism "infection by contiguity." A second mode of involvement they designated as "infection by implantation," in this instance using the

phrase in its usual definition. They considered this form to be practically limited to the lower lobe bronchi. In the upper lobes they designated the mucosal and submucosal involvement as "infection by continuity."

Pathologic Study. In order to obtain data on the frequency of tuberculous tracheobronchitis and to demonstrate, if possible, its pathogenesis, a study was made of the clinical records, protocols and microscopic slides of 122 cases of pulmonary tuberculosis coming to autopsy. The only selective criteria employed in isolating this group were: (1) That the primary cause of death should have been the tuberculosis and (2) that permission for complete autopsy had been obtained. Thus a series was obtained complete with respect to tissues from the larynx, trachea, bronchi and bronchial lymph glands, in addition to representative blocks from all involved regions of the lungs.

One or 2 sections from the larynx, 1 to 3 from the trachea and 1 each from the large bronchi and bronchial lymph glands were prepared, the blocks being selected to show any gross lesion. If no such lesion were apparent, then the blocks were chosen at random from the regions cited.

Statistical Study. Since such material at once raises a question concerning the adequacy of the sampling, especially in the trachea where the area is large, the entire respiratory tracts from 8 fatal cases of pulmonary tuberculosis were isolated and 12 transverse serial blocks made from each trachea. The blocks were numbered consecutively from above downward. One section was prepared from each block and examined for evidence of tuberculosis, routine hematoxylin and eosin stains being employed. A trachea was recorded as tuberculous in which any section exhibited histologic signs of the disease.

The results of this study (Table 1) disclosed a marked tendency for tuberculous involvement, when it occurs, to be spread over the

TABLE 1.—PULMONARY TUBERCULOSIS. TUBERCLES IN SERIAL BLOCKS OF TRACHEA (TEST SERIES).

Serial levels.	Autopsy No.							
		A-223-AG.	A-309-AG.	A-36-AJ.	A-351-AH.	A-236-AL.	A-289-AL.	A-78-AK.
1	.	—	—	—	+	—	—	+
2	.	—	—	—	+	—	+	+
3	.	—	—	—	+	—	+	+
4	.	—	—	—	+	—	+	+
5	.	—	—	—	+	—	+	+
6	.	—	—	—	+	—	+	+
7	.	—	—	—	+	—	+	+
8	.	—	—	+	+	—	—	+
9	.	—	—	—	+	—	—	+
10	.	—	—	+	+	—	+	+
11	.	—	—	+	+	—	+	+
12	.	—	—	—	+	—	+	+

entire tracheal mucosa. This was further emphasized by the distribution of the tubercles which tended to be moderately uniform with respect to successive levels. Furthermore, in this test series, as well as in the larger series generally, the tuberculous involvement appeared to be chiefly in the posterior wall. Well over two-thirds of the tubercles were to be found in the posterior one-half of the trachea.

It is evident that in 5 of the tracheas of this series the random selection of any one of the 12 sections would completely represent the entire trachea with respect to the presence or absence of tuberculosis, assuming, for simplification, that the 12 sections themselves completely represented the trachea. In 2 cases some of the sections exhibited tubercles, while others of the series did not.

If agreement between the individual section and the character of the series from one trachea be considered a success, and a disagreement a failure in the probability sense, then of the 84 sections there are 71 successes and 13 failures. The probability that a section chosen at random will accurately describe the entire trachea with respect to the presence or absence of tubercles is $\frac{71}{84}$ or 0.845 ± 0.026

where 0.026 is the probable error of the prediction $(0.6745 \sqrt{\frac{pq}{n}})$.

Since in the larynx and bronchi one section represents a much greater proportion of the total tissue, the probability of accurate representation by a single section taken at random must necessarily be considerably higher.

The high prediction value of a single section is but another way of expressing a fact consistently appearing throughout this study: that when the tracheal mucosa, in fatal cases of pulmonary tuberculosis, succumbs to the tubercle bacillus, the yielding of the defenses tends to be general so that the entire mucosa, or a large portion of it, becomes involved practically simultaneously.

TABLE 2.—PULMONARY TUBERCULOSIS. MUCOSAL LESIONS. 122 AUTOPSIES.

Region.	Incidence of tuberculosis.	
	No.	Per cent.
Larynx	37	30.4
Trachea	25	20.5
Bronchi	41	33.6
Tract generally (larynx and/or trachea and/or bronchi) .	59	48.4
No involvement of tract	63	51.6

In Table 2 is given the incidence of lesions in the various regions. Involvement of some portion of the larynx, trachea or large bronchi occurring in 48.4% of the cases. The observed lesions were grossly ulcerative much more frequently in the larynx than in the trachea and bronchi.

The complete distribution of the cases with respect to the various combinations of involvement is given in Table 3. In Tables 4 and 5, the same form is utilized for the segregation of the cases showing or failing to show miliary dissemination. The further statement of the statistical character of the various groups appears in Table 6 where the mean and standard deviation are given for each combination.

TABLE 3.—PULMONARY TUBERCULOSIS. MUCOSAL LESIONS. 122 AUTOPSIES.

Larynx.	Trachea.	Bronchi.	No. of cases.		
			Male.	Female.	Total.
—	—	—	38	25	63
—	—	+	11	3	14
—	+	—	3	1	4
—	+	+	0	4	4
					— 85
+	—	—	7	2	9
+	—	+	5	6	11
+	+	—	4	1	5
+	+	+	6	6	12
			—	—	— 37
			74	48	122

TABLE 4.—PULMONARY TUBERCULOSIS. MUCOSAL LESIONS. AUTOPSIES. 27 MILIARY CASES.

Larynx.	Trachea.	Bronchi.	No. of cases.		
			Male.	Female.	Total.
—	—	—	11	10	21
—	—	+	2	0	2
—	+	—	1	1	2
—	+	+	0	0	0
					— 25
+	—	—	0	1	1
+	—	+	0	0	0
+	+	—	1	0	1
+	+	+	0	0	0
			—	—	— 2
			15	12	27

TABLE 5.—PULMONARY TUBERCULOSIS. MUCOSAL LESIONS. AUTOPSIES. 95 NON-MILIARY CASES.

Larynx.	Trachea.	Bronchi.	No. of cases.		
			Male.	Female.	Total.
—	—	—	27	15	42
—	—	+	9	3	12
—	+	—	2	0	2
—	+	+	0	4	4
					— 60
+	—	—	7	1	8
+	—	+	5	6	11
+	+	—	3	1	4
+	+	+	6	6	12
			—	—	— 35
			59	36	95

TABLE 6.—PULMONARY TUBERCULOSIS. 122 AUTOPSIES.

Males.					Females					Totals.				
No. of cases.	Age at death, yrs.		Duration, mos.		No. of cases.	Age at death, yrs.		Duration, mos.		No. of cases.	Age at death, yrs.		Duration, mos.	
	Mean.	S.D.	Mean.	S.D.		Mean.	S.D.	Mean.	S.D.		Mean.	S.D.	Mean.	S.D.
59	33.7	14.2	26.1	29.1	36	<i>Non-miliary Cases.</i>				95	30.2	14.6	25.8	26.8
						24.6	13.4	25.4	22.7					
15	30.9	20.7	10.2	8.8	12	<i>Miliary Cases.</i>				27	24.5	19.4	8.3	7.6
						16.4	14.2	6.0	4.7					
74	33.1	15.8	22.8	26.9	48	<i>All Cases.</i>				122	29.0	16.0	21.9	24.9
						22.5	14.0	20.5	21.5					

Superficially, it would appear that the mean ages at death for the females is appreciably different in the miliary and non-miliary groups while the corresponding figures for the males show no such differences. However, if this is considered as a problem in random sampling with selection of groups of 36 and 12 from such a population of 48, it develops that the distribution of the means of such samples would have the following statistical character:

Arithmetic mean	22.52 years
Standard deviation	3.54 "
Skewness	0.0

From this it follows that the actual mean of 24.56 years for the age at death in the non-miliary cases differs from the mean of all random samples by 0.577 standard unit,* that is, the difference in age at death between the miliary and non-miliary groups of females could occur by chance about once in two times. Clearly this difference is insignificant.

When the same analysis is applied to the corresponding male group the same result is obtained, t being 0.602.

With respect to sex there is a very significant difference between the mean age at death for the males compared with the females. Not only does our autopsy series show a marked preponderance of males over females in numbers, but the average age at death for the males greatly exceeds that for the females. While these differences are statistically significant and cannot be ascribed to chance, we have no reason to consider them other than the result of pre-selection in the patients referred to the tuberculosis unit of our hospital.

When duration of the disease is considered there is again a very significant difference for both sexes. Those cases terminating in miliary dissemination consistently show short durations of the disease, duration here being the time elapsing from the first recognizable sign or symptom of pulmonary tuberculosis until death.

* The standard variate t is: $t = \frac{\bar{v} - M_v}{\sigma_v}$

Associated, in our opinion, with the short duration in those cases terminating in a miliary dissemination is the relative infrequency of tracheobronchial mucosal involvement in this group, only 5 out of 27 cases showing any lesions whatever. To compare with this, we find that in 95 non-miliary cases, 45 had involvement of the mucosa of the trachea or bronchi.

These 2 groups of cases differ by another factor in addition to duration of the disease. The miliary group is composed of those with proved hematogenous dissemination. The infrequency of involvement of the tracheobronchial mucosa in the miliary group further indicates that the hematogenous route is of no consequence in the establishment of these lesions.

Further examination of these data emphasizes the marked tendency for lesions of the larynx, trachea and bronchi to occur concomitantly. The concurrence of tracheal lesions with laryngeal tuberculosis has led some to the mistaken conclusion that the tracheal involvement is secondary to that of the larynx. If this were true, absence of laryngeal lesions would imply absence of tracheal lesions, a conclusion contrary to fact. In this series there were 8 instances of tracheal tuberculosis in which the larynx was entirely free of such lesions.

The fallacy of considering tracheobronchial mucosal lesions secondary to laryngeal tuberculosis arises from the failure to realize that strong positive correlations do not necessarily imply causal relationship. Events may occur together, not because they are causally related, but because they are all associated with a common factor. In this specific problem the common factor is pulmonary tuberculosis.

Histologic Observations. Inspection of the tracheal and bronchial sections showed that if only 1 or 2 tubercles occurred, these usually were to be found in the posterior portion, and where there were many lesions they were most numerous in this region. Furthermore, the great majority of these lesions were to be found very intimately associated with the mucous glands, either in conjunction with the ducts or in relationship to the secreting alveoli. The lesions were thus relatively superficial.

The usual form of the lesion was that of the small epithelioid tubercle with caseating center. The cellular infiltrate consisted of both polymorphonuclear and mononuclear cells, the former being especially abundant when the tubercle lay close beneath or actually involved the mucosal epithelium. Very small ulcers were found to be associated with immediately subjacent epithelioid tubercles. In larger ulcers showing more tissue destruction no such relationship could be demonstrated. About such lesions, once established, a marked tendency to lateral extension beneath the epithelium was observed, so that ulcerated regions were frequently underlain by more widely extensive tuberculous involvement than the actual

area of ulceration would suggest. Both the tuberculous and non-tuberculous mucous glands showed dilatation of the ducts with markedly increased mucin formation, many neutrophils being free in the secretion.

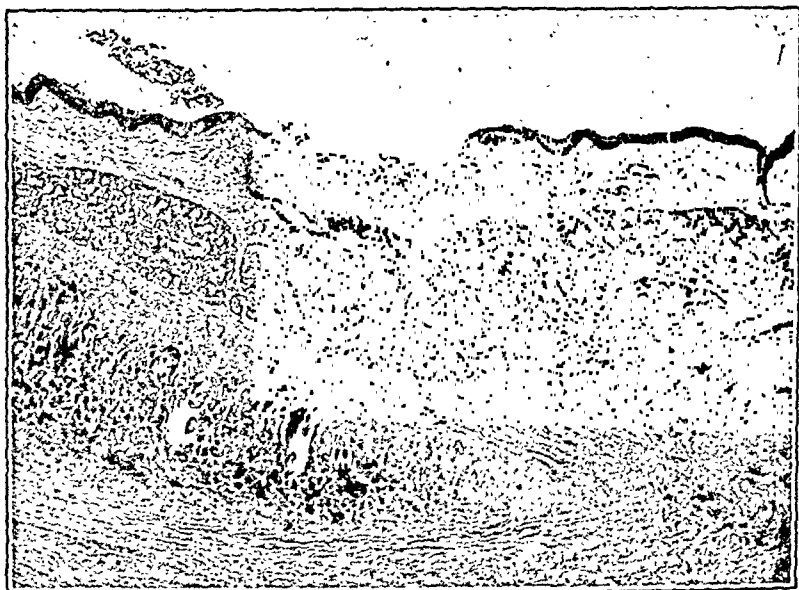


FIG. 1.—Ulcerative tuberculous tracheitis. Small mucosal lesion associated with involvement of mucous glands of posterior portion of trachea. ($\times 20$.)



FIG. 2.—Ulcerative tuberculous bronchitis. Marked thickening of mucosa. Early stenosis. ($\times 10$.)

In addition to the granulomatous lesions, in all instances a diffuse chronic inflammation, with edema and fibrosis, was to be found. This process, etiologically not definitive, resulted in thickening of the submucosa to a marked degree, especially in the bronchi where the lumen was frequently sensibly reduced.

The portal of entry of the process in the bronchi is difficult to determine with accuracy. In many instances continuity of tuberculous involvement from nearby lymph nodes to the peribronchial tissues should be readily demonstrated, making entirely reasonable the view that such infections arise by transport of the organisms through the lymphatics from the peribronchial tissue to the submucosa, or by way of the deeply lying mucous glands to the mucosa.

In the trachea, however, this confusion of possible routes was not found to exist. In no instance of tracheal tuberculosis was there diffuse peritracheal tuberculosis and, in many cases, tracheal mucosal lesions occurred without tubercles being found in the nearby peritracheal lymph glands. One is forced to the conclusion that extension from the peritracheal tissues, by any route whatever, is an unimportant mechanism. When it is considered that most of the bronchial lesions were of the same type as seen in the trachea, one is less convinced of the soundness of the argument that such lesions arise predominantly by invasion of the peribronchial tissues.

The incidence of open ulcers depends upon the definition of such a lesion, particularly with respect to size. In 2 instances the entire tracheobronchial mucous membrane had been destroyed, with a continuous tuberculous granulation tissue surface replacing the mucosa throughout the tract. In other instances the areas of ulceration were microscopic and unappreciable to the naked eye. Between these extremes, all gradations in size could be found. The incidence of ulceration, reported for any such series, is thus likely to be dependent upon the circumstances of observation.

Summary. From the data presented it is evident that the occurrence of tracheal tuberculosis is unrelated to hematogenous dissemination. It is further not associated with peritracheal extensions, since many instances of mucosal tuberculosis were found in which both the peritracheal connective tissue and the adjacent lymph glands were entirely free of evidences of the disease.

On the contrary, there was observed a marked tendency for the simultaneous occurrence of tubercles in all portions of the trachea. Further, such lesions exhibited a definite tendency to more frequent occurrence posteriorly in patients who had been recumbent for prolonged periods. These lesions, in their earliest stages, were intimately in association with the mucosal epithelium or the ducts of the mucous glands. With the further observation that all the cases exhibited a sputum rich in tubercle bacilli, we are led to the conviction that the tracheal involvement is predominantly, if not entirely, a matter of implantation or contact infection.

Since, in many of the main bronchi, lesions of the same character were found as in the trachea, it is a reasonable presumption that the same mechanism tends to prevail in these regions. In view of the instances of proved continuity of involvement from the peribronchial tissue, however, it cannot be denied that bronchial mucosal tuberculosis may arise by direct extension from lesions in neighboring peribronchial structures. The latter mechanism appears to be much more important in the intrapulmonary bronchial branches than in the main bronchi.

While tuberculous tracheobronchitis is not causally related to laryngeal tuberculosis, they tend to be concurrent, so that in this series 76% of the cases with tuberculous laryngitis had also involvement of the trachea or bronchi. Where the larynx was free from the disease, 25% of the cases had lesions in the lower portion of the tract. Considering the trachea alone, the above figures become 46% and 9.4%, respectively.

In this autopsy series, while evidences of fibrosis and thickening of the tracheal and bronchial submucosæ were marked, no conclusive evidence of a healed ulcer was discovered, although some of the localized changes were compatible with this interpretation.

In the entire series no instance of presumptive primary tracheal tuberculosis occurred. We are inclined to doubt the existence of such an entity.

Conclusions. 1. In a series of 122 cases of pulmonary tuberculosis studied at autopsy, 50 cases (41%) showed lesions in the trachea, main bronchi or both.

2. The mode of infection of the tracheal mucosa is outstandingly one of contact with bacillary sputum.

3. The immediate portal of entry in the trachea may be either through the epithelium or by way of the ducts of the mucous glands.

4. Infection of the mucosa of the main bronchi is predominantly one of contact, but in an appreciable number of instances the invasion is by direct extension from the peribronchial structures.

5. The complication occurs more frequently in cases in which the pulmonary disease is of long duration.

6. Laryngeal tuberculosis is frequently concurrent with tracheobronchial mucosal spread but not causally related to it.

7. Involvement of the tracheobronchial mucosa, when it occurs at all, tends to be widespread and most marked along the posterior wall.

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OBSERVATIONS ON THE USE OF CARBON DIOXIDE IN EARLY PNEUMONIA.

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INHALATION of carbon dioxide, diluted either with oxygen or merely with air, is now a well-established therapeutic and prophylactic measure in surgery to prevent or counteract pulmonary complications,^{4c} and in obstetrics to overcome neonatal atelectasis.^{4a} Its chief value lies in inducing such an inflation of the lungs that the airways are cleared, natural drainage established and the lungs freed of infective matter.⁵ In internal medicine and pediatrics, on the contrary, inhalation of carbon dioxide has not yet received a sufficient trial to determine to what extent it may be of value also in these fields, particularly at the onset of pulmonary infection.

In justification of a trial of this inhalation in early pneumonia, it may be recalled that this therapy has largely eliminated the post-operative pulmonary complications that were formerly grouped indiscriminately under the term "postoperative pneumonia," regardless of whether they were merely atelectatic or truly pneumonic. It has not only made the problem of initiating respiration in the asphyxial newborn far simpler for the obstetrician than it formerly was, it has given him the most effective means now known of combating the tendency to subnormal respiration, cyanosis and the development of pneumonia, particularly in weak or premature babies that formerly induced a considerable mortality.²

Internists have been disinclined to the idea that inhalation of carbon dioxide might be of value in the treatment of pneumonia, on the ground that mere deep breathing would obviously be incapable of removing the consolidated exudate of the pneumonic lung as seen at autopsy.* But if inhalation of carbon dioxide has any value, it lies primarily in the prevention of that accumulation of exudate before its consolidation, that is, before the ill effects of occlusion have had time to reach full development. If bronchial occlusion is the critical factor in the accumulation of exudate that

* Coryllos, in a recent personal communication, has observed that carbon dioxide liquefies pneumonic exudate with great rapidity *in vitro*.

an increasing number of observers claim, it is of prime importance that the airways should be kept open. And only three means are now known to open and clear the airways, and thus establish drainage: 1, by use of the bronchoscope; 2, by frequent changes of the patient's position, and, 3, by inhalation of carbon dioxide.

Whatever the method employed there are already grounds worthy of serious consideration indicating that clearing of the airways in the early stages of pneumonia may abbreviate or even abort the disease. Henderson,^{4b} who has been chiefly responsible for the introduction of the inhalational method of resuscitation from asphyxia and for the relief of postoperative pulmonary complications, has truly said that at least in all secondary pneumonias "internists would do well to borrow from surgery one of its major axioms: a well-drained infection is relatively harmless; an occluded infection is always dangerous." Coryllos¹ has demonstrated experimentally that bronchial occlusion may be a factor of critical importance in the development of an acute pulmonary infection. And Chevalier Jackson⁶ has demonstrated clinically that the use of the bronchoscope early in pneumonia may produce a rapid recovery.

Not every hospital has in its service a skilled bronchoscopist. But in every hospital now there is an anesthetist who is conversant with the administration of carbon dioxide; and it is a technique that the internist easily acquires.

Comparison of Treatments. These considerations seemed to the writers to afford an adequate basis for the trial clinically of the administration of carbon dioxide to such cases of pneumonia as came to the hospital in the early stages of the disease. And we report herewith the results of our observations.

As a background we present in Section A of Table 1 the mortality during 5 years of the pneumonia patients who came under our observation and who received no inhalational treatment. In Section B of that table is shown the mortality of patients who early in the disease received inhalation of oxygen, or of carbogen (5% carbon dioxide in oxygen) by means of a tent. Little or no hyperpnea was thus induced. This group also includes those patients who received carbon dioxide inhalational therapy more than 72 hours after the onset of illness. In Section C are given the comparable figures for patients who were early treated with brief but repeated inhalations of carbon dioxide in sufficient concentration to induce marked temporary hyperpnea. The mortalities in the 3 groups were: (a) For those without inhalation, 17%; (b) for those with early inhalation of oxygen or carbogen or inhalation of carbon dioxide late in the illness, 16%; and (c) for those with early inhalation of carbon dioxide, 4%.*

* This series originally included 121 patients in the untreated (A) and 48 patients in the treated group (C). Of these 9 were excluded in the first and 1 in the last group. These patients were primarily treated for heart failure, but died with a terminal pneumonia. If these patients were included in the statistics the mortalities would read 23.1% in Group A and 6.4% in Group C, respectively.

TABLE 1.—CASES OF BRONCHOPNEUMONIA AND LOBAR PNEUMONIA AND THOSE WHO DIED (A) WITH NO CO₂ INHALATIONAL TREATMENT; (B) WITH INHALATION OF OXYGEN OR CARBOGEN (5% CARBON DIOXIDE IN OXYGEN) OR CO₂ LATER THAN 48 HOURS AFTER ONSET, OR WHEN ADMINISTERED IN QUANTITIES INSUFFICIENT TO CAUSE VENTILATION; AND (C) WHEN CARBON DIOXIDE WAS ADMINISTERED EARLY BY THE METHOD HERE DESCRIBED.

REGISTERED DATA BY THE MEMBERS OF THE BOARD OF HEALTH

Treatment.		W = Months of November to April, inclusive. S = Months of May to October, inclusive.										Total.	Mortality, %.
		1931.		1932.		1933.		1934.		1935.*			
		W	S	W	S	W	S	W	S	W	S		
(A)	Broncho-	3	4	19	7	10	7	9	2	7	7	75	17.0
	Lobar	5	0	8	3	3	0	7	3	5	3	37	
	Total	8	4	27	10	13	7	16	5	12	10	112	
	Deaths:												
	Broncho-	1	0	3	1	0	2	1	0	1	1	10	
	Lobar	0	1	1	0	1	0	2	1	2	1	9	
	Total	1	1	4	1	1	2	3	1	3	2	19	
(B)	Broncho-	1	1	8	7	4	2	1	1	2	2	29	
	Lobar	0	0	2	1	2	1	1	0	1	0	8	
	Total	1	1	10	8	6	3	2	1	3	2	37	
	Deaths:												
	Broncho-	0	1	1	0	1	1	0	0	1	0	5	
	Lobar	0	0	0	0	0	1	0	0	0	0	1	
	Total	0	1	1	0	1	2	0	0	1	0	6	
(C)	Broncho-	2	0	6	4	3	6	6	1	3	2	33	4.3
	Lobar	0	1	3	1	3	1	2	0	2	0	13	
	Total	2	1	9	5	6	7	8	1	5	2	46	
	Deaths:												
	Broncho-	0	0	0	0	0	0	0	0	0	1	1	
	Lobar	0	0	0	0	0	0	1	0	0	0	1	
	Total	0	0	0	0	0	0	1	0	0	1	2	

* Figures for 1935 are for the first 8 months only.

Equally favorable to this treatment are the figures for the days that hyperpyrexia continued in these three classes of cases, as shown in Table 2 for Group A (no inhalational CO₂ therapy), Table 3 for Group B (inadequate inhalational CO₂ therapy), and Table 4 for Group C (adequate inhalational CO₂ therapy). In the cases of bronchopneumonia the three classes had an average duration of fever of (a) 11.5 days, (b) 10.3 days and (c) 4.3 days, respectively. In the cases of lobar pneumonia the figures were (a) 13.7 days, (b) 11.7 days and (c) 5.2 days of fever, respectively.

Technique of Inhalation. The patients who received no inhalation were for the most part those who were not seen early enough for us to hope that this treatment would be effective. Others who were seen early enough, however, were given the conservative oxygen inhalational and symptomatic treatment. Otherwise they were entirely comparable to cases to which inhalation was administered.

The cases treated with early inhalation of oxygen showed, as might be expected at that stage of the disease, no perceptible effect (Table 2). Those treated early with carbogen also were only slightly affected, and as this inhalation is relatively expensive it was abandoned (Table 3). Our observations should not, however, be interpreted as weighing against the administration of either oxygen or carbogen for the relief of anoxia in later stages of pneumonia.

The advantages in using carbon dioxide alone are many: It is inexpensive; it comes in small tanks that are easily transported; and it can be administered to the patient without the discomfort

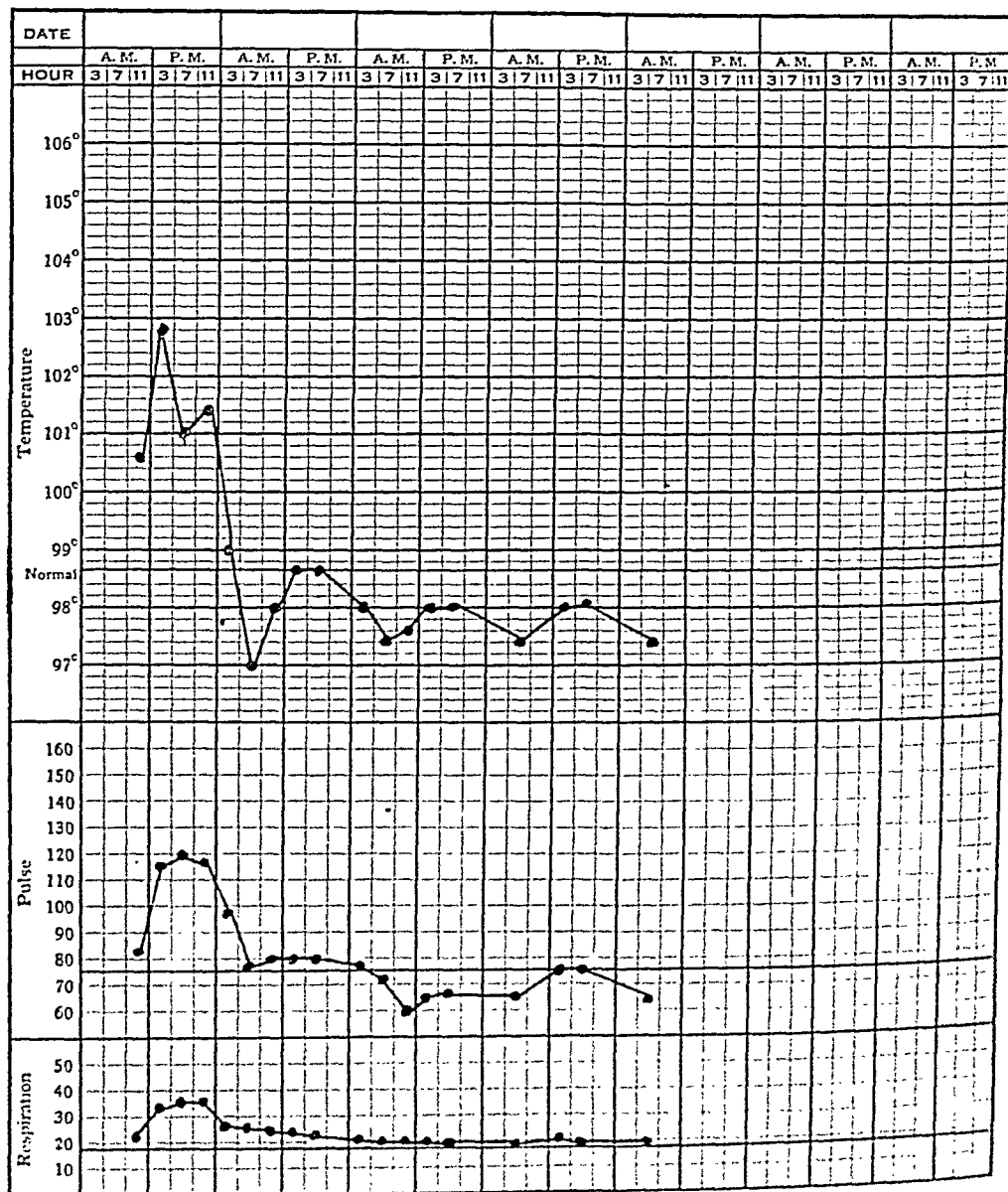


FIG. 1.—Case 16788. Male, aged 20; bronchopneumonia. Upper respiratory infection for 10 days. Cough, weakness, fever and blueness of lips was then noted. On examination: Temperature, 102.8° F.; pulse, 20; respiration, 32. Cyanotic and dyspneic; dullness at left base with patchy areas of diminished breath sounds and voice sounds. Fine rales at both bases. Patient looked very ill, and prognosis was charted as guarded. Urine, negative. W.B.C., 18,700. Polys., 77.5. Treatment: (CO₂) inhalations every hour while awake, and every 2 hours during the night. Crisis Within 24 hours. Notes: Symptomatic improvement took place next day. Lungs cleared up 6 days after admission.

TABLE 2.—DAYS OF DURATION OF FEVER IN 112 PATIENTS WHO RECEIVED NO CO₂ INHALATIONAL TREATMENT, OF WHOM 93 RECOVERED AND 19 DIED.

Days of fever.	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
Broncho-	0	1	3	5	6	4	7	6	0	8
deaths	0	1	1	0	2	2	0	0	0	0
Lobar	0	0	0	1	1	4	8	3	3	1
deaths	0	0	0	0	1	2	3	1	1	1
Total cases	0	1	3	6	7	8	15	9	3	9
Total deaths	0	1	1	0	3	4	3	1	1	1
Days of fever.	11.	12.	13.	14.	15.	16.	17.	18.	19.	20.
Broncho-	5	2	6	6	1	1	2	1	1	1
deaths	0	0	0	1	0	0	0	0	0	0
Lobar	3	1	3	1	0	0	0	0	1	1
deaths	0	0	0	0	0	0	0	0	0	0
Total cases	8	3	9	7	1	1	2	1	2	2
Total deaths	0	0	0	1	0	0	0	0	0	0
Days of fever.	21.	22.	23.	24.	25.	26.	28.	30.	40.	90.
Broncho-	1	3	1	1	0	1	0	0	1	0
deaths	0	2	0	0	0	0	0	0	0	0
Lobar	1	0	0	1	2	0	1	1	0	1
deaths	0	0	0	0	1	0	0	0	0	0
Total cases	2	3	1	2	2	1	1	1	1	1
Total deaths	0	2	0	0	1	0	0	0	0	0

Average days of fever: Bronchopneumonia, 11.5; lobar pneumonia, 13.7.

and sometimes the anxiety that the use of a tent involves. In all of our cases this gas was administered by the "drip" method introduced by Dr. Arthur Guedel for the prevention of postoperative pulmonary complications in this hospital.* The technique is as follows:

A linen towel is folded in half, along its length. It is then wrapped around the patient's head and face from the chin to the

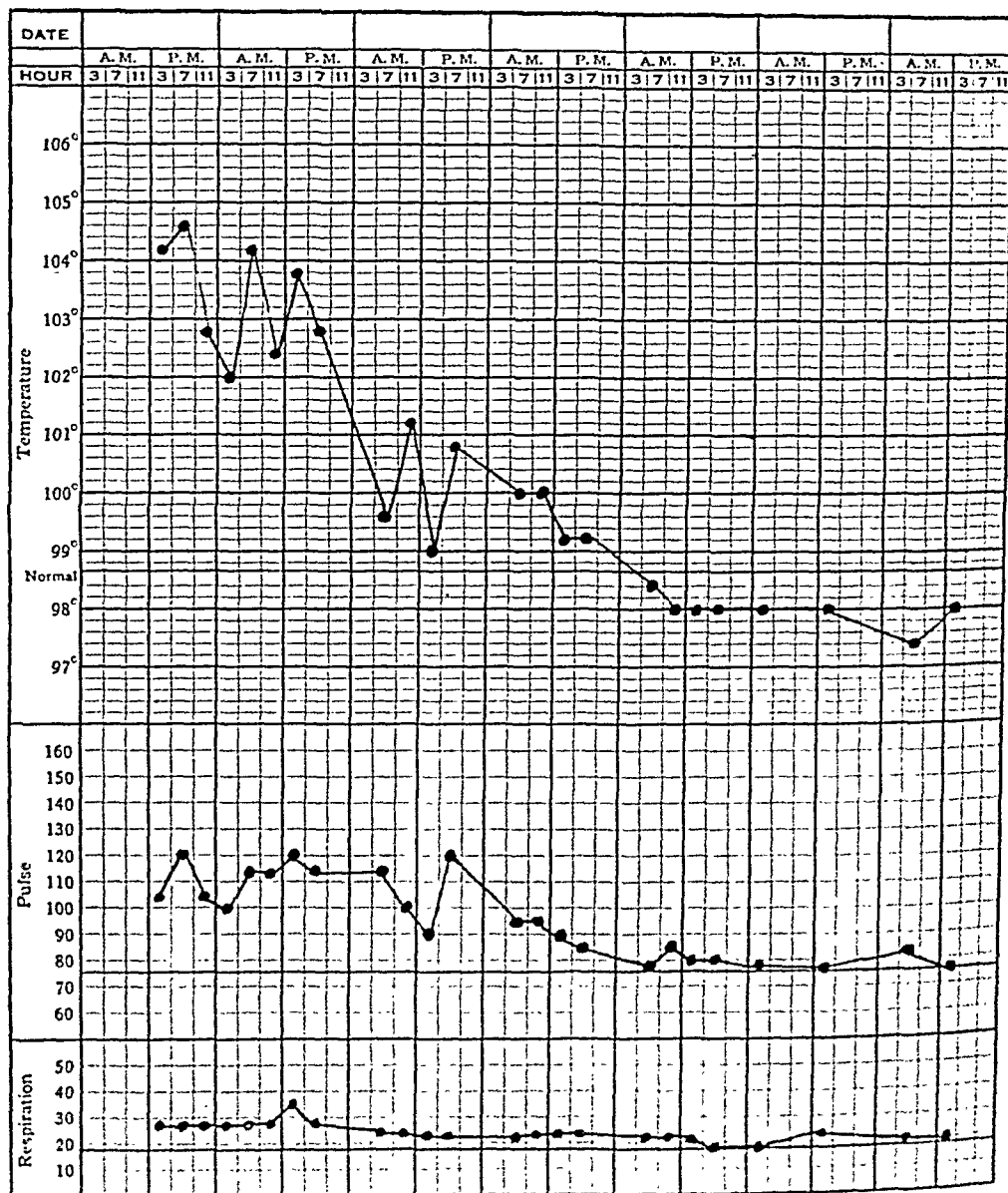
TABLE 3.—DURATION OF FEVER (DAYS) IN 37 PATIENTS TREATED WITH OXYGEN OR CARBOGEN (5% CARBON DIOXIDE IN OXYGEN) OR CO₂ ADMINISTERED IN MOST INSTANCES LATER THAN 48 HOURS AFTER ONSET, OR EARLIER IN QUANTITIES INSUFFICIENT TO CAUSE VENTILATION, OF WHOM 31 RECOVERED AND 6 DIED.

Days of fever.	5.	6.	7.	8.	9.	10.	11.	12.	14.	15.	16.	17.	19.	20.	28.	30.
Broncho-	1	1	2	3	1	3	2	2	3	3	2	1	2	1	2	1
Deaths	1	0	1	2	0	0	0	0	1	0	0	0	0	0	0	0
Lobar	0	1	0	0	2	0	0	1	1	1	0	1	0	0	0	0
Deaths	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total cases	1	2	2	3	3	3	2	3	4	4	2	2	2	1	2	1
Total deaths	1	1	1	2	0	0	0	0	1	0	0	0	0	0	0	0

Average days of fever: Bronchopneumonia, 10.3; lobar pneumonia, 11.7.

vertex, so that a shallow cup is formed with the face as the base and the towel forming the sides. The gas is run at the rate of about 3 liters per minute. In the absence of a flow meter, a steady, soft stream which hits the hand without force generally suffices. The patient is instructed to open the mouth and breathe deeply.

* Quantitative apparatus and an open mask from designs of Dr. Yandell Henderson are made by the Foregger Company, New York, and the Ohio Chemical and Supply Company, Cleveland.



The end of the flexible rubber tube is held about 2 inches over the tip of the nose. The gas is then allowed to run until the patient develops a hyperpnea which the observer can see is wholly out of voluntary control. The hyperpnea is continued under the gas for about 1 minute when the administration is discontinued, but the towel around the face is not removed. The hyperpnea continues for 1 minute or 2 after the gas is stopped. The patient is then allowed to rest from 3 to 5 minutes, and a similar hyperpnea is again induced. Two such periods of hyperpnea constitute a treatment. This double inhalation is repeated at intervals of 3 hours during the waking hours and usually once or twice at night when the patient awakens. The administration of the gas is continued until the temperature becomes normal.

Immediate Effects of the CO₂ Inhalation. The inhalation of carbon dioxide gas was begun in most instances *within the first 48 hours after onset of symptoms.*

The following is the usual sequence of events when the gas is given: after the first few breaths the patient involuntarily coughs several times. After the administration of the gas is completed a severe paroxysm of coughing may appear, during which the patient brings up surprisingly large amounts of yellow pus.* Soon afterward he falls asleep, apparently in a state of exhaustion, but awakens later with a feeling of well-being and of being refreshed all out of proportion to the degree of illness which was present several hours before. From the time of the first inhalation of the gas the patients of their own accord state that they feel much better.

TABLE 4.—DURATION OF FEVER (DAYS) IN 46 PATIENTS TREATED WITH EARLY INHALATION OF CARBON DIOXIDE IN QUANTITIES SUFFICIENT TO CAUSE VENTILATION, OF WHOM 44 PATIENTS RECOVERED AND 2 DIED.

Days of fever.	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	14.
Broncho-pneumonia	2	7	8	5	3	0	3	1	0	2	0	1
deaths	0	0	1	0	0	0	0	0	0	0	0	0
Lobar	1	1	2	4	2	0	2	0	0	0	1	1
deaths	0	0	0	0	0	0	0	0	0	0	1	0
Total cases	3	8	10	9	5	0	5	1	0	2	1	2
Total deaths	0	0	1	0	0	0	0	0	0	0	1	2

Average days of fever: Bronchopneumonia, 4.3; lobar pneumonia, 5.2.

Appearance of Clinical Improvement. Within the first 24 to 48 hours most of the patients showed a marked decrease in toxicity, and by the time the fever abated they looked and felt well enough to get out of bed, even though the physical signs of the disease in the chest were still present and in some cases continued for 6 to 15 days after defervescence was completed. Although clinical improvement may thus appear very early, physical signs of resolution might not appear for from 3 to 5 days after the first adminis-

* This pus is, at first, viscid and thick, but later becomes thin and more liquid in consistency.

tration of gas. Figs. 1, 2 and 3 show typical temperature charts in bronchopneumonia and lobar pneumonia, treated with early inhalation of carbon dioxide.

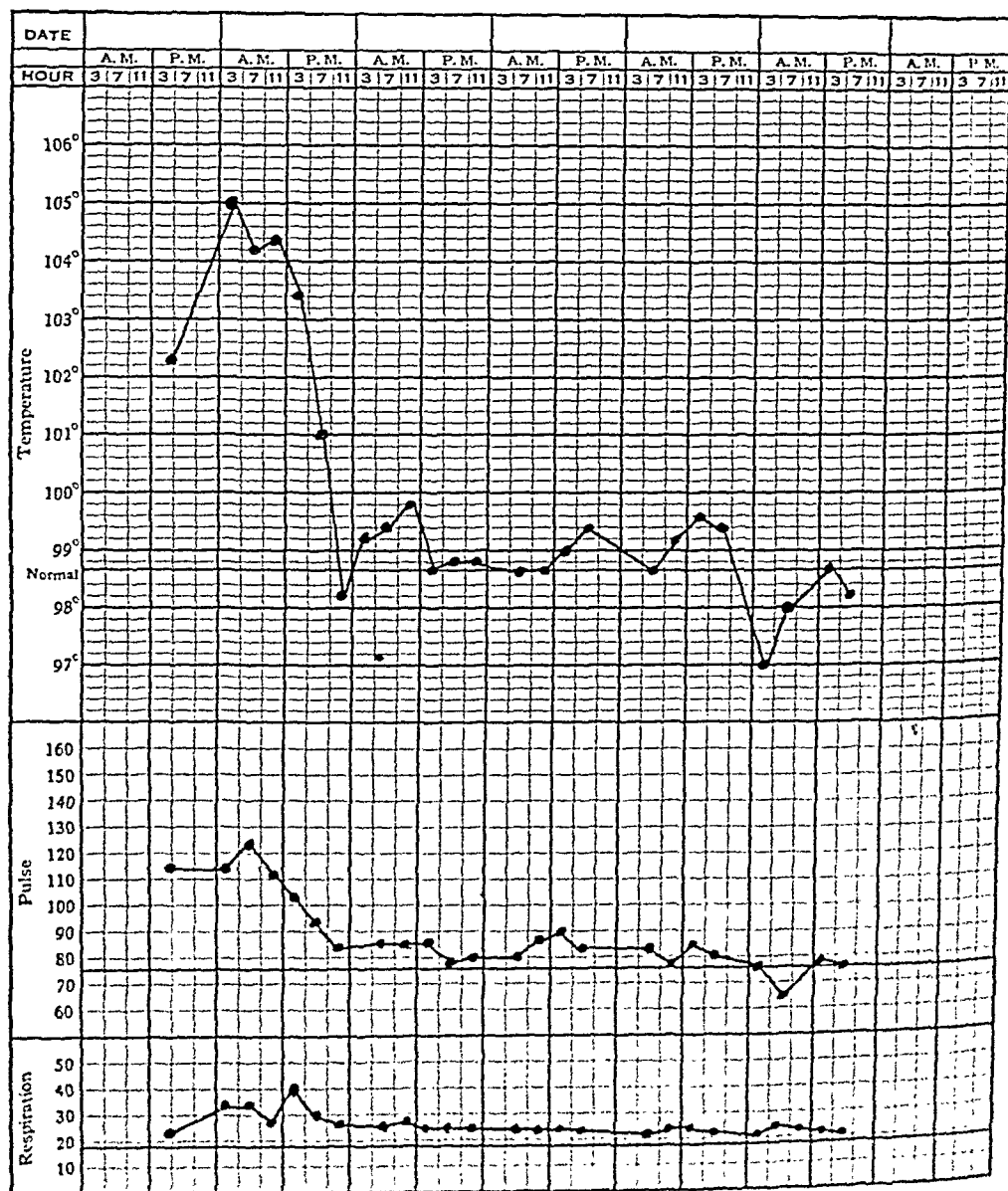


FIG. 3.—Case 21040. Male, aged 15; lobar pneumonia. Upper respiratory infection for 3 days prior to admission, when patient developed pneumonia. On examination: Temperature, 102.4° F. On admission, he showed cyanosis, diminished expansion at the right base with dullness; absent breath sounds and fine crackling rales. Roentgen ray examinations revealed infiltration at the base of the right lung. Treatment: Carbonic acid gas inhalations were started 12 hours after entry, and given every hour by day and every 3 hours at night. Crisis took place 12 hours after the therapy was commenced. Notes: Symptomatic improvement was noted on the second day. The chest was clear in 9 days.

Complications and Contraindications. Untoward results of the administration of the gas were noticed in 2 patients. In both instances it was noted that these patients developed a facies strongly resembling the mask facies of encephalitis and 1 of these patients complained of diplopia. In both instances, however, all symptoms and signs disappeared within the next 2 days and the patients appeared normal thereafter. The patient who developed a subjective diplopia suffered from a lobar pneumonia and received the inhalations at 2-hour intervals. The other patient was a very small woman who was receiving the gas at 3-hour intervals.

Two failures were observed in the entire adequately treated series (Group C). One was a patient with diffuse bilateral bronchopneumonia which involved most of both lungs. The defervescence did not occur as anticipated. The patient was extremely ill but she recovered. The second patient, who had a lobar pneumonia was the 81-year-old woman who also suffered from heart disease. One cannot say whether or not the administration of the gas played a rôle in these recoveries. However, the main contraindication for the use of carbon dioxide gas would appear to be in instances of patients suffering from myocardial insufficiency.

Some Reasons for Inadequate Therapy and Poor Results. This series³ included patients whose ages ranged from 47 days (with recovery) to 89 years (with a death). The greatest source of error lies in the failure to continue the inhalation until a true hyperpnea takes place. The second source of trouble is the failure adequately to space the hyperpnea reactions to intervals of 3 to 4 hours. Poor results were commonly obtained in the use of carbogen gas (5% carbon dioxide in oxygen). This gas cannot be given in adequate concentrations by the open or drip method to produce the necessary ventilation, and if used at all, it must be given with a mask by the closed method as one does in administering an anesthetic gas. The greatest drawbacks in the use of carbogen are (1) the frequency of administration that is necessary and (2) the great expense involved.

In the authors' experiences, as well as those reported personally to them by other physicians, it was found that the inhalation of the gas cannot be given successfully to patients who suffer from myocardial insufficiency. Such patients develop a distressing dyspnea consisting of shallow rapid respiration which does not adequately ventilate the lungs.

Summary. In the observed cases of pneumonia here reported, the defervescence appeared in 87% of the patients within 1 to 7 days. The average duration of fever was 4.3 days for bronchopneumonia and 5.2 days for lobar pneumonia. The toxicity of the illness disappeared within 24 to 48 hours. The first administration of the gas caused a coughing reflex of severe nature after which copious amounts of purulent material were expectorated. Exhaustion and refreshing sleep followed. Resolution of the disease process appeared in from 3 to 5 days after the administration of the gas.

The physical signs in the chest persisted for several days after the temperature became normal. The mortality rate of the group treated by early inhalation of CO₂ was 4% as compared with 17% on the group receiving no CO₂ inhalations.

It must be emphasized here that these observations were made in patients in whom the disease was diagnosed, and the treatment begun in most instances within 48 hours after onset of the first symptoms.

Conclusions. 1. The administration of carbonic acid gas shortens the course of both bronchopneumonia and lobar pneumonia, particularly the former, the average days of fever being 4.3 days for bronchopneumonia and 5.2 days for lobar pneumonia.

2. The defervescence occurs rapidly in either type of pneumonia.

3. The mortality is definitely diminished and compares most favorably with that of other established methods of treatment.

4. The early administration of carbonic acid gas is a valuable therapeutic measure in the treatment of pneumonia.

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THE INADEQUATE TREATMENT OF EARLY SYPHILIS.

CLINICAL RESULTS IN 409 PATIENTS.

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PREVIOUS studies of the end results following the inadequate treatment of early syphilis have been based upon patients who returned to the clinic because of ailments due or thought by them to be due to their previous infection, or who were discovered when they returned for reasons unrelated to their earlier complaints. It is recognized that these patients include only a small proportion of individuals insufficiently treated for early syphilis, and that the ultimate outcome of the large majority who lapse before treatment is completed cannot be determined with any degree of accuracy. The most important reasons for this are: (1) While the average patient with a genital sore or a persistent skin eruption usually suspects he has syphilis, and may apply directly for treatment, he

is much less familiar with the manifestations of late syphilis, and if he becomes ill, may seek medical attention anywhere; (2) since the Wassermann test is not a routine procedure, unless he presents a classical picture of the disease in its late stages, or returns to the clinic or physician where he was first treated, the relation of his old infection to his presenting complaints may not be detected; and (3) many patients who remain symptom-free, or who develop benign skin or bone syphilis, never return for medical care.

It appeared, therefore, that a review of the patients coming to this clinic might throw some light on the ultimate outcome following inadequate treatment for early syphilis. The publicity of the Institute repeatedly stresses the necessity for continuous treatment, particularly of early syphilis. As a result many patients are examined who have no specific complaints, but who are interested in learning whether they have been cured or if further treatment is necessary. The difference between this material and that reported in other studies is in the inclusion of a large number of individuals who, remaining well, would probably not have given further thought to their infection had it not been forcibly brought to their attention.

Material and Methods. The material was obtained by reviewing all of the admissions during the period from January 1, 1933, to December 31, 1934. From these records a selection was made of all white male patients over 16 years of age, with a reliable history of acquired infection, who had received inadequate treatment for early syphilis, and who were examined at this clinic after an interval of at least 1 year from the last treatment. Patients were excluded who on reexamination presented negative clinical and serologic findings but whose spinal fluid had not been analyzed. On the other hand, patients with serologic or clinical evidence of syphilis on reexamination were included even though a spinal fluid examination had not been obtained. By inadequate treatment for early syphilis is meant the administration of less than 20 injections of a trivalent arsenical and of a heavy metal within a period of 1 year, this amount having been administered during the first 2 years following infection. A total of 409 patients were found to fulfill the above criteria, and it is on this group that the present report is based.

Evaluation of Treatment Results. In evaluating the final outcome, two classifications were employed, that is, "result satisfactory" and "result unsatisfactory." The latter group comprised those patients who developed clinical or serologic recurrences at any time following the institution of early inadequate therapy. The "result satisfactory" group includes patients observed for at least 1 year after the end of treatment, during which time no symptoms of syphilis developed and the blood serologic reaction was persistently negative. Moreover, all patients in this group had negative physical and spinal fluid examinations at the end of the year or thereafter.

In a few instances the χ^2 test of homogeneity⁷ has been employed to analyze the results statistically.

Comparative Results According to the Diagnosis at the Time Treatment Was Begun. Table 1 presents an analysis of the results of inadequate therapy according to the stage of the disease when treatment was started. The usual diagnostic classes are shown. In addition to these, there were 72 patients who received their first treatment in the primary stage, but who either had no Wassermann examination at the time or, if this was performed, its result could not be ascertained. These patients have been classified as sero-unknown primary syphilis. This group was included in the series in spite of the uncertainty regarding the Wassermann reaction, because subsequent observations revealed that the large majority, that is, 64 (89%) developed clinical or serologic evidence of syphilitic infection.

TABLE 1.—RESULTS ACCORDING TO STAGE IN WHICH TREATMENT WAS BEGUN.

Result.	Sero-negative primary.		Sero-positive primary.		Sero-unknown primary.		Total primary.		Secondary.		Early latent.*		Total.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Satisfactory	17	80.9	69	37.5	8	11.1	94	33.9	34	31.2	6	26.1	134	32.8
Unsatisfactory	4	19.1	115	62.5	64	88.9	183	66.1	75	68.8	17	73.9	275	67.2
Total	21	100.0	184	100.0	72	100.0	277	100.0	109	100.0	23	100.0	409	100.0

* First 2 years of infection.

It is seen that 17 (80.9%) of the 21 patients first treated in the sero-negative primary stage had a satisfactory outcome. The frequency of satisfactory results in the seronegative primary patients was statistically significantly greater than that in each of the other 3 groups, but the difference between any 2 of the latter 3 was not statistically significant, probably due to insufficient numbers. This comparison does not include the sero-unknown primary group. However, the results show a progressive decrease in the incidence of arrest and cure, and a progressive increase in the incidence of recurrences, with increasing intervals from the date of infection to the beginning of therapy. This finding is, of course, not novel, since it is now an accepted principle in the modern treatment of syphilis. What is deserving of special comment, however, is the fact that this result occurred, even though all patients received inadequate therapy. The data of Moore and Kemp,⁶ when recalculated on the basis of inadequate treatment, point to a similar conclusion. It is apparent that whether or not a patient expects to or can continue throughout a prescribed régime of adequate therapy, the earlier the diagnosis is made and treatment instituted, the more favorable is his prognosis.

Comparative Results With Continuous and Discontinuous Treatment Systems. Continuous treatment is here defined as the uninterrupted administration of an arsenical or a heavy metal or both. Patients whose treatments did not fall into this category received "discontinuous" treatment. Subdivisions into intermittent and irregular treatment schedules were not attempted, since by so doing the size of the resulting classes would have been diminished, and the significance of the findings decreased.

The influence of continuous and discontinuous treatment régimes on the ultimate outcome is shown in Table 2. Satisfactory results were obtained in 78 (42.2%) of the continuous treatment group, as compared with only 56 (25%) of patients whose treatment system was discontinuous; the difference between these two values is statistically significant. The superior results of continuous treatment are evident regardless of the stage of the disease when therapy was begun. Statistical analysis also indicates that a significantly larger proportion of patients in the satisfactory outcome group (78 out of 134, or 58.1%) received continuous treatment than the comparative proportion in the unsatisfactory result group (107 out of 275, or 38.9%). On the basis of these findings, a patient with early syphilis should be placed on a continuous therapy régime, for even though he should lapse before receiving adequate treatment, his chances for an ultimate satisfactory outcome are greater under such a régime than they would be under any other system.

TABLE 2.—RESULTS ACCORDING TO TYPE OF TREATMENT—CONTINUOUS OR DISCONTINUOUS.

Treatment system.	Result	Seronegative primary.		Seropositive primary.		Sero-unknown primary.		Total primary.		Secondary.		Early latent.*		Total.	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Continuous	Satisfactory	14	93.3	41	43.6	5	21.7	60	45.4	12	33.3	5	35.7	78	42.2
	Unsatisfactory	1	6.7	53	56.4	18	78.3	72	54.6	26	66.7	9	61.3	107	57.8
	Total	15	100.0	94	100.0	23	100.0	132	100.0	38	100.0	14	100.0	185	100.0
Discontinuous	Satisfactory	3	50.0	28	31.1	3	6.1	34	23.4	21	30.0	1	11.1	56	25.0
	Unsatisfactory	3	50.0	62	65.9	46	93.9	111	76.6	49	70.0	8	88.9	165	75.0
	Total	6	100.0	90	100.0	49	100.0	145	100.0	70	100.0	9	100.0	221	100.0
Total		21	100.0	184	100.0	72	100.0	277	100.0	108	100.0	23	100.0	406	100.0

* First 2 years of infection.

Results According to Amounts of Treatment. In grouping the treatment schedules so as to indicate the number of doses without regard to their continuity or lack of continuity, "much" here signifies 15 or more injections when referring to an arsenical, and 10 or more when referring to a heavy metal. "Little" indicates less than these

amounts. In the text the first of the two adjectives refers to arsenical and the second to heavy metal. Thus "much-little" signifies much arsenical, little heavy metal.

The clinical results according to varying amounts of inadequate treatment are shown in Table 3, which is based on the entire group without regard to the stage of infection when therapy was instituted. The comparative values for the different diagnostic classes were identical with those shown in the table, and for this reason only the summated findings are presented.

TABLE 3.—RESULTS ACCORDING TO AMOUNTS OF TREATMENT.

Result.	Little-little.		Little-much.		Much-little.		Much-much.		Total.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Satisfactory	58	26.7	32	32.7	23	44.2	21	50.0	134	32.8
Unsatisfactory	159	73.3	66	67.3	29	55.8	21	50.0	275	67.2
Total	217	100.0	98	100.0	52	100.0	42	100.0	409	100.0

See text for definition of terms "little-little," "little-much," etc.

Treatment successes ranged from a low of 58 (26.7%) of 217 patients receiving little-little therapy, to a high of 21 (50%) of 42 receiving much-much therapy. The difference between these two values is highly significant statistically. Little-little therapy was represented in a statistically significantly smaller proportion of treatment success than treatment failure cases. Thus 58 (43.3%) of the 134 patients in the satisfactory outcome group received this amount of treatment as compared with 159 (57.8%) of the 275 in the treatment failure group. Moreover, the frequency of cases in the satisfactory outcome group given much-much therapy (21 out of 134, or 15.7%) was significantly greater than the frequency of patients in the unsatisfactory outcome group who had been treated with similar amounts of an arsenical and of a heavy metal (21 out of 275, or 7.6%). The evidence thus indicates that even though treatment may be inadequate according to the standards now generally accepted, the incidence of successful results increases with increasing amounts of therapy.

Analysis of Unsatisfactory Results. The patients who experienced an unsatisfactory outcome were classified as follows: (1) Wassermann recurrent latent syphilis. (2) Early infectious relapse. (3) Central nervous system syphilis. (4) Cardiovascular syphilis. (5) Late benign and visceral syphilis.

Table 4 presents an analysis of the observed recurrences based on varying amounts of treatment for early syphilis. Summating

the three types of late syphilis having serious import, that is, neurosyphilis, cardiovascular syphilis, and late benign and visceral syphilis, the combined incidence of these recurrences in the different treatment groups was as follows: little-little, 50.7%; little-much, 36.7%; much-little, 32.7%; and much-much, 33.4%.

TABLE 4.—ANALYSIS OF RECURRENCES ACCORDING TO VARYING AMOUNTS OF TREATMENT.

Treatment.	Little-little.		Little-much.		Much-little.		Much-much.		Total.	
No. of patients.	217		98		52		42		409	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Wassermann recurrence	52	23.9	31	31.6	13	25.0	4	9.5	100	24.5
Early infectious relapse	8	3.7	3	3.1	4	9.5	15	3.7
Central nervous system	72	33.2	22	22.4	16	30.8	11	26.2	121	29.6
Cardiovascular	26	12.0	11	11.2	3	7.2	40	9.8
Late benign and visceral syphilis	12	5.5	3	3.1	1	1.9	16	3.9
Total recurrences	170	78.3	70	71.4	30	57.7	22	52.4	292	71.4
Cases with 1 recurrence	159	73.3	66	67.3	29	55.8	21	50.0	275	67.2
Cases with more than 1 recurrence	11	5.1	4	4.1	1	1.9	1	2.4	17	4.2

An analysis of the incidence of these three serious late sequelæ according to the stage of the disease when treatment was initiated showed the same comparative results for each type of systemic involvement. In each case the incidence was lowest in the seronegative primary group, much higher in the seropositive primary group, and still higher in secondary syphilis patients. The frequency of each of these three recurrences then fell off slightly in the group with early latent syphilis. These findings are well shown by the combined values: seronegative primary, 9.5%; seropositive primary, 34.2%; secondary, 45.9%; and early latent, 39.1%.

The most important type of unsatisfactory result from a public health viewpoint is that of infectious relapse. The incidence of this condition was 3.7%, which is much lower than the 13.3% frequency observed by Moore and Kemp in their inadequately treated group, and also lower than the 13.1% incidence among inadequately treated patients in the Coöperative Clinical Group material.⁵ It is of interest to note also that the percentage of neurosyphilis is appreciably less than that reported by Kemp and Menninger⁴ in inadequately treated patients (43.4%) and in untreated patients (52.6%). Since only 56 of the 100 patients with Wassermann recurrent latent syphilis had a spinal fluid examina-

tion in all probability the 29.6% represents the minimum of neurosyphilis. By the same token, the percentage of latent syphilis is probably lower than that shown by our figures. The incidence of cardiovascular syphilis among these patients is slightly lower than that observed by Kemp and Cochems.³ It seems probable that the incidence of each of these recurrences is lower than that reported by other investigators because of the inclusion in this material of a large group of symptom-free patients who ordinarily do not report to the physician or clinic for reexamination.

The Satisfactory Result Group. Table 5 represents an analysis of the 134 patients classified as "result satisfactory." Every patient included in this group had a negative spinal fluid examination. Thirty-four (25.3%) were observed for periods ranging from 1 to 4 years after the last treatment; 58 (43.3%) of the 134 patients were observed for from 10 to 15 years and more after the last treatment, the longest interval being 30 years. Of this group, 32 (55.2%) had negative Roentgen ray and electrocardiographic examinations.

TABLE 5.—THE INTERVAL BETWEEN LAST TREATMENT AND FINAL OBSERVATION IN 134 SATISFACTORY RESULT CASES.

Interval in years.	1	2-4	5-9	10-14	15+	Total.
No. of cases	5	29	42	31	27	134
Per cent of total . . .	3.7	21.6	31.3	23.1	20.2	100.0
Negative Roentgen ray and electrocardiogram	2	7	23	18	14	64
Negative provocative.	1	11	16	11	8	47

The first 2 years following cessation of treatment is the critical period so far as infectious relapses are concerned. In the Coöperative Clinical Group material,¹ 91% of all infectious relapses occurred during this interval. The comparative value obtained in the present study was 86.7%. The great majority of patients in the "satisfactory result" group were, therefore, well outside this danger zone, for 117 (87.3%) had been observed for periods exceeding 2 years after the cessation of treatment.

The probability that any of these 117 patients might later develop central nervous system involvement is exceedingly remote, for it is now recognized that a negative spinal fluid examination 2 years or more after infection assures the patient of subsequent normal spinal fluid findings, except under very unusual circumstances. The situation is quite different with respect to cardiovascular syphilis. A negative cardiovascular examination is no guarantee against future involvement of this system. In the Coöperative Clinical Group material of 186 cases of uncomplicated aortitis where the duration of infection was known, there were 90% in which the process had developed to the point of detection later than 5 years from infection.² Aortic regurgitation was noted most frequently in the period 20 to 30 years from infection. It is thus apparent that, excluding late skin and bone tertiaryism, the most serious danger confronting the satisfactory result group is the possibility of subsequently developing cardiovascular recurrence.

However, the chances are overwhelmingly in favor of a continued state of health in patients who are clinically and serologically negative 5 years and more after the cessation of treatment, and such patients comprised 74.5% of our group.

The individual who maintains clinical and serologic negativity for varying periods following the last treatment is naturally desirous of knowing whether he is likely to continue so throughout life. This information is highly desirable to the clinician, also, especially with reference to the patient known to have been inadequately treated for early syphilis. Shall further treatment be instituted as an added protection against late serious recurrences, or do the physical discomfort, financial stress, and even danger of antisymphilitic measures to the patient outweigh any possible benefits he may derive? With this question in mind, a selection was made of all patients who were subjected to a complete reëxamination one or more years following a negative physical, blood and spinal fluid examination. Only 43 such cases were found. In each instance the reëxamination conducted from 1 to 25 years after the first negative survey was also negative, and each of these 43 patients is included in the satisfactory result group. These findings indicate the comparative security which a patient with negative findings may enjoy, but it should be emphasized that the small size of the group prevents any sweeping generalizations.

Discussion. The observation that 134 (32.8%) of the patients in this series achieved a satisfactory result in spite of early inadequate treatment is deserving of special comment. The question arises whether this percentage represents a fair approximation of the satisfactory result cases in a large population of inadequately treated patients. At the outset it must be admitted that the asymptomatic patient generally has no reason to enter a hospital, so that reports emanating from such institutions do not give a true picture of the situation. This is a valid objection to the findings of Stokes and Des Brisay,⁸ who observed clinical, spinal fluid and serologic negativity in only 17 (8.4%) of 178 inadequately treated syphilitics. Their result is based on a selected group of individuals, that is, those who reported to a hospital for the relief of symptoms, the syphilitic infection being discovered through routine diagnostic procedures. Is our material characterized by a bias in the opposite direction, and does this account for our higher percentage of satisfactory results?

It is our impression that this is not the case. In the first place, it will be recalled that the series does not include a large number of patients who were clinically and serologically negative, but whose spinal fluid had not been examined. Had this examination been conducted, a large majority would have been found to have negative spinal fluids, and this would have placed them in the satisfactory result group. This alone, other factors being equal, would have produced an incidence of satisfactory results higher than that reported.

Moreover, each patient in the satisfactory result group came to

the clinic because of his own knowledge of an antecedent infection, and not because he was compelled to seek relief for distressing symptoms. Such individuals are generally not included in hospital statistics because they are not components of the average hospital population. The objection may be raised that if it is true that a hospital group does not consist of a representative sample of asymptomatic syphilitics, by the same token it is comprised of a higher proportion of the general population of patients with symptomatic recurrence than is found in our material. This objection is based on the premise that more patients with serious recurrences are seen in the hospital than in an ambulatory clinic. While no actual data can be given on this point, attention should be called to the fact that many of our symptomatic patients were hospitalized on our recommendation, and furthermore, that many patients returned to us for follow-up care after their acute siege in a hospital had subsided. With the exception of a very small percentage of individuals who are rushed to a hospital as a result of sudden crucial symptoms, there to die, the clinic at one time or another probably sees the great majority of patients with serious symptomatic recurrence.

In conclusion, it should be emphasized that these results are not to be interpreted as a brief for inadequate treatment. The recommendations of the Coöperative Clinical Group and of the Health Organization of the League of Nations should be rigorously followed, and any physician responsible for the inadequate treatment of early syphilis is remiss in his duty to both patient and public.

Summary. A study was made of the outcome in 409 patients who had received early inadequate treatment for syphilis. Patients were classified as "result satisfactory" if they presented no evidence of syphilis as determined by clinical, serologic and spinal fluid tests one year or more after the last treatment; and as "result unsatisfactory" if they developed clinical, serologic, or spinal fluid signs of syphilis at any time following the cessation of treatment.

With regard to the diagnosis when treatment was begun, the highest proportion of satisfactory results was noted in the seronegative primary stage.

A significantly higher incidence of satisfactory results was observed among patients who had received continuous treatment than in those treated by other systems.

Much arsenical was defined as 15 or more injections of a trivalent preparation and much heavy metal as 10 or more injections of bismuth or mercury. Treatment successes were lowest in the group receiving less than these amounts of both drugs, and highest in those treated with these amounts or more.

Central nervous system syphilis comprised the largest proportion of late relapses. Wassermann recurrent late syphilis had a slightly lower incidence and cardiovascular syphilis still lower. Early infectious relapse and late benign and visceral syphilis had an equal and also the lowest incidence.

The 134 patients classified as result satisfactory were followed for from 1 to 30 years after the last treatment; 117 (87.3%) of these had been observed for periods longer than 2 years after the cessation of specific medication. It was pointed out that the most serious danger confronting these patients was the possibility of subsequently developing cardiovascular recurrence.

Of the 409 patients comprising this study 32.8% achieved a satisfactory result. An analysis was made of the sampling factors which might have been influential in producing this proportion of favorable results. It appeared that this value probably represents a fair approximation of the incidence of satisfactory result cases in a large population of patients inadequately treated for early syphilis.

It was emphasized that although inadequate treatment does produce a certain proportion of successful results, adequate treatment schemes as recommended by the Coöperative Clinical Group and by the Health Organization of the League of Nations should be rigorously followed in the management of early syphilis.

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AN EXPERIMENTAL STUDY OF THE VARIATIONS IN THE PRODUCTION OF VISUAL DISTURBANCE BY CERTAIN NEW CINCHONA DERIVATIVES.

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THE frequency of visual damage following therapeutic use of certain cinchona alkaloids, especially of ethylhydrocupreine, is attested by a large number of case reports, groups of clinical cases

and experimental data in animals,⁹ as well as by personal experience. The pathologic lesions responsible for loss of vision is recognizable both by means of the ophthalmoscope and by microscopic tissue section, and has been adequately described.⁴ There is a fair amount of evidence pointing toward the factor of individual idiosyncrasy.⁵ However, the exact mechanism producing the lesion is not agreed upon. It is believed by some to be direct toxic action on the retinal cells but other evidence points toward primary spasm of retinal arteries resulting either from direct action of the compounds as vasoconstrictors, or, as recently suggested by Wolff,¹¹ the retinal vascular spasm may be the result of depressed tissue oxidation.

During the course of a more extensive experimental and clinical investigation of a large number of cinchona alkaloids,^{*6} an attempt has been made and is herewith reported to estimate the toxicity to the visual apparatus of certain of these alkaloids which have a high pneumococidal power and a general toxicity low enough to justify consideration of their clinical use in pneumococcal pneumonia.

Experimental. The work of Smith and Fantus¹⁰ suggested that in the perfused peripheral vessels of the frog ethylhydrocupreine possessed greater vasoconstricting properties than quinine. Using the alkaloids in concentrations approximating 1:2000 (M/648, monohydrochloride), the only definite finding so far in the present work is that peripheral vasoconstriction in the frog appears to be a general reaction of cinchona bases. It has been obtained with quinine, apocupreine (apoquinine), ethylapocupreine, ethylhydrocupreine and its d-rotatory isomer ethylhydrocupreidine, and with hydroxyethylapocupreine. It seems not invariably to be obtained with any of these substances. Thus, with hydroxyethylapocupreine, of 12 preparations perfused as indicated, 4 did not show definite persistent constriction; with ethylhydrocupreine the corresponding figures were 4/10, with quinine 1/12. The Ringer formula was NaCl 6.5, KCl 0.14, CaCl₂ (anhydrous) 0.24, NaHCO₃ 0.2 gm. per liter. The cannula insertion was through ventricle into bulbous. It may be that under some set of conditions this method might prove of use for attack on the problem of cinchona amblyopia, but at present it appears less promising than the direct method.

A direct attack on the problem of cinchona amblyopia was made by eye examination following injection of quinine, ethylapocupreine and ethylhydrocupreine subcutaneously in the frog.⁵ These doses were 0.01 to 0.02 cc. M/20 dihydrochloride per gram and were definitely in the lethal range. No changes definitely attributable to the injections were noted in the eye grounds.

Preliminary observations were then made on dogs injected intraperitoneally with ethylhydrocupreine. It was not found possible to give doses exceeding 84 mg. (expressed as dry base) per kg. by this route without fatality, and eye changes were not marked (Table 1). Much larger doses were, however, tolerated by subcutaneous injection. A mid-dorsal, rather than a flank, site was chosen to avoid the chance of direct penetration of solution into the body cavity, with possible alteration of rate of absorption and visceral damage.¹ The plan, therefore, gradually developed of giving

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a single mid-dorsal subcutaneous injection of a large dose, 0.25 to 0.50 mg. mol. dihydrochloride per kg. The surviving dogs were observed for varying periods, up to 49 days, then killed. The eyes were removed at once and fixed, one in Zenker's solution and one in the following mixture: absolute alcohol by volume, 6 parts; chloroform, 3 parts; glacial acetic acid, 1 part. The Zenker-fixed tissue was stained with hematoxylin and eosin, the specially fixed tissue with toluidine blue and phloxine, both from paraffin-embedded material.

Ophthalmoscopic Findings. Minor grades of visual damage were naturally not certainly detectable by ophthalmoscopic examination. Dogs with serious visual disturbance generally showed pallor of the disc at the time or within a few days later. Pupils of such dogs were usually dilated and responded sluggishly to light. Retinal arterial constriction was difficult to assess.

Microscopic Findings (Table 1). These were identical with those of Forster⁴ and previous workers referred to by him.

TABLE 1.—EFFECTS OF CINCHONA BASES ON DOG EYE.

Dog No.		Dose, Mg., dry base/K.	Visual disturbance.	Ophthalmoscopic change.	Microscopic change.	Days after injection.
2*	Ethylhydrocupreine	42*	None	Doubtful	Slight	1
8*	Ethylhydrocupreine	42*	Slight	Slight	Slight	5
9*	Ethylhydrocupreine	42*	None	Doubtful	Slight	5
3*	Ethylhydrocupreine	63*	None	Doubtful	Slight	1
6*	Ethylhydrocupreine	37 x 7 daily	None	Slight	Doubtful	8
11	Ethylhydrocupreine	170	Blind 5th day	Marked	Marked	11
13	Ethylhydrocupreine	170	Blind 1st day	Marked	Marked	2
10	Ethylhydrocupreine	212	Blind 2d day	Marked	Marked	7
16†	Ethylapocupreine	169	Blind 1st day	Marked	Marked	49
17	Quinine	162	Blind 2d day	Marked	Marked	41
C-3	Hydroxyethylapocupreine	88	None	None	None	28
27	Hydroxyethylapocupreine	132	None	None	None	17
28	Hydroxyethylapocupreine	132	None	None	None	10
C-2	Hydroxyethylapocupreine	132	None	None	None	28
26	Hydroxyethylapocupreine	177	None	None	None	17
C-1	Hydroxyethylapocupreine	177	Questionable	None	Very slight	28
30	Hydroxyethylapocupreine	177	None	None	None	9
31	Hydroxyethylapocupreine	177	None	None	None	14
32	Hydroxyethylapocupreine	177	None	None	None	14
33	Hydroxyethylapocupreine	177	None	None	None	14
37	Hydroxyethylapocupreine low rotating fraction	100	None	None	None	14
35	Hydroxyethylapocupreine low rotating fraction	167	None	None	None	14
23‡	Quinidine	81	None	Doubtful	Very slight	6
24	Isopropylapocupreine	132	Blind 6th day	Marked	Marked	14
25	Isopropylapocupreine	176	Blind 2d day	Marked	Marked	14
34	Butoxyethylapocupreine	145	None	None	None	11
38	Butoxyethylapocupreine	145	None	None	None	6
36§	Butoxyethylapocupreine	194	None	8

N.B. "C" dogs injected in Laboratory of Pharmacology, University of Chicago.

* Intraperitoneal injection; the rest subcutaneous.

† Dogs 14 and 15 not notably affected by same dosage; observed 5 and 6 days respectively. Eyes not removed.

‡ Dog 22 killed by same dosage.

§ Dog 36 developed distemper and only microscopic observations were made.

1. Eyes from 10 control dogs showed normal retina, choroid and sclera.

2. No visible change in the blood-vessels was seen in *any* section of eye of *any test or control* animal. In the test animals, the changes were confined to the retina proper.

3. In those test animals showing changes, destruction of cells of the ganglion layer predominated, the number of destroyed cells varying from a few to all ganglion cells. In those dogs allowed

to survive for ten days or more, any ganglion cells remaining were in a state of good preservation. Dogs killed before the tenth day showed, in addition, some edema of retina and an occasional lymphocyte or polymorphonuclear leukocyte. Occasional changes in the cells of the bipolar layer were seen in the more severely damaged eyes.

Other Observations. Local necrosis, which appears to be a general reaction to subcutaneous injection of cinchona bases (Dawson and Bodansky),² was noted rather frequently in the form of a sloughing of the skin at the site of injection. It seems to have nothing to do with eye changes, and does not appear to influence the general health. Dogs which following injection presented persistent drug toxicosis or were for any other reason in poor condition, were sacrificed to prevent postmortem eye changes before fixation. Some of the periods of observation were, therefore, rather short. In Dogs 11 and 17 there seemed to be some possible lessening of the amblyopia 24 and 35 days, respectively, after injection.

Cinchona bases seem to be well absorbed from subcutaneous injection in spite of the possibility of local necrosis. Thus, Dogs 19, 20 and 21 were all killed by a dose of 101 mg. quinidine base per kg., M/S solution in the calculated amount of standard HCl; Dogs 12 and 18 were similarly killed by M/4 solutions of ethylhydrocupreine and quinine, the doses of anhydrous base being 170 and 162 mg. per kg., respectively.

Statistical Calculation of Significance of Results. If we arrange two groups of dogs on the basis of probable essential difference in chemical formula and approximately similar handling, we have in Group 1 Dogs 11, 14, 15, 16, 17, 24, 25, receiving cinchona alkaloids of abbreviated formula RO.B, where B stands for "base" and RO for alkoxy side chain; in Group 2, Dogs C1, C2, 26, 27, 28, 30, 31, 32, 33, 35, formula HORO.B for hydroxy-alkoxy side chain. The results may be set up as in Table 2.

TABLE 2.—EFFECT OF INTRODUCTION OF BETA HYDROXYL RADICAL INTO ALKYL OF CINCHONA ALKOXY SIDE CHAIN ON TENDENCY TO PRODUCE BLINDNESS IN DOGS.

Group.	Side chain.	Dosage mg. per kg.	Observed for days.	Blind.	Not blind.	Total.
1 . . .	RO	132-176	5 or more	5	2	7
2 . . .	HORO	132-177	9 or more	0	10	10
				Total	5	12
					12	17

While the numbers involved are small, they are yet obviously suggestive of substantially less danger of visual damage from hydroxyethylapocupreine than from the group "RO" alkaloids. Calculation by the "Exact" method of Fisher,³ Section 21.02, shows that the probability of such a set of results being due to chance is only 1 in 294.

Discussion. It may seem surprising that there should be any difference in action on the retina of two substances so closely alike in chemical formula as ethyl- and hydroxyethylapocupreine. Young

and Loevenhart,¹² however, noted the production of optic lesions in the rabbit by organic arsenicals with an amino or substituted amino group in the para position to the arsenic, but not with the amino or substituted amino group in the ortho or meta position.

The results of the "dog test" described have already been utilized.⁷ Owing to its serious eye effects in dogs, isopropylapocupreine was excluded from clinical trial while hydroxyethylapocupreine, owing to its lack of such effects in dogs, has been introduced. Both of these drugs previously had appeared desirable on the ground of *in vitro* and *in vivo* pneumococcicidal activity displayed by the methods used by Maclachlan, Permar, Johnston and Kenney.⁶ While further work may cause a revision of opinion, this test seems likely to open up an avenue of approach somewhat safer than any previously available in the field of chemotherapy of pneumonia.

Summary. 1. An effort has been made to develop a method for the estimation of the property of visual damage possessed by certain cinchona alkaloids which are under investigation as to their possible therapeutic use in pneumococcus pneumonia.

2. Results of perfusion experiments in the frog with a number of cinchona alkaloids suggested that under the conditions used, peripheral vasoconstriction is a general reaction of cinchona bases. For attack on the problem of cinchona amblyopia this method appears at present less promising than the direct method.

3. Observation and histologic study of the eyes of dogs subcutaneously injected with large doses of these alkaloids indicate a distinct difference in their behavior with regard to retinal damage. The ganglionic layer was found damaged by ethylhydrocupreine, ethylapocupreine, isopropylapocupreine, and quinine. Comparable dosage with hydroxyethylapocupreine in 10 dogs caused no demonstrable damage. The difference in results appears to be statistically significant and coincides with clinical observations in man to be reported at a later date.

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SOMATIC PHENOMENA IN PSYCHONEUROSES.

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ALTHOUGH the scientific method (cause-effect) is by convention employed in most medical research, certain difficulties in the study of psychoneuroses preclude its employment there. First of all, despite the observation of Pavlov⁷ and his pupils⁸ of psychoneurosis-like states in animals used for the study of conditioned reflexes, it may be said that a true psychoneurosis is peculiar to man. Second, our present day concept of the pathogenesis and etiology of psychoneurosis makes it obvious that its deliberate production in any man is unwarranted. Hence, any study of the psychoneuroses must be made as they spontaneously present themselves. In making such a study one may describe and classify the observed phenomena, reason slowly backwards from effect to cause and then direct therapeutic efforts towards the alteration of the hypothesized cause. If therapeutics of this type results in cure in a sufficient number of instances, one may infer that the hypothesis is established.

The diagnosis of psychoneurosis is made always by exclusion. It is necessarily preceded by a thorough physical examination supplemented by any indicated studies, and if the latter prove negative, thus ruling out organic disease, one is justified in surmising that psychic factors are responsible for the derangement in function or for the symptoms of which complaint is made. The probabilities of the correctness of this surmise becomes even greater, if emotional conflicts, unhappiness and the like are found in the patient's history. If a therapeutic attack upon these emotional conflicts results in a restoration to normal function and a disappearance of symptoms, the probability of the validity of the cause—effect reasoning process becomes greater still. Certainty is attained, however, only after one has studied a sufficiently large series of cases to rule out the possibility of fallacy in the inductive process.

The foregoing suggests some of the pitfalls lying ahead of one who attempts to study any aspect of the psychoneuroses. Such study can be made only by the employment of effect—cause reasoning upon the phenomena observed and by the employment of the therapeutic test upon the hypothesized cause. This method has been employed throughout the present study, and we have endeavored to bear in mind its inherent limitations.

The material for this study consisted of a group of 20 patients on whom the diagnosis of psychoneurosis was made after a careful history and physical examination supplemented by any indicated tests had excluded organic disease; 11 of these patients were women; 9 men. Their average age was 29 with variations between 24 and 32.

The presenting symptoms which occurred most frequently are shown in Table 1.

TABLE 1.—PRESENTING SYMPTOMS IN 20 PSYCHONEUROTIC PATIENTS.

	Per cent.		Per cent.
Fatigue	90	Dyspnea	70
Digestive complaints	90	Headache	70
Excessive perspiration	90	Precordial discomfort	60
Coldness of extremities	90	Insomnia	60
Tachycardia	80		

The physical examination supplemented by laboratory studies revealed but slight variation from the normal average. Those findings deserving special mention are shown in Table 2.

TABLE 2.—OBJECTIVE FINDINGS IN 20 PSYCHONEUROTIC PATIENTS.

Low blood pressure	100	Lymphocytosis (above 35%)	85
Sugar tolerance definitely increased (low curve)	90	Low basal metabolism (below -5)	85
Moist skin	85	Coldness of extremities	75
Tenderness over colon in L. L. Q.	85	Cyanosis or "marbling" of extrem- ities	70

Further evidence of similarity in these patients became manifest when attention was focussed upon the psychic background. All were unhappy; all were dissatisfied with life. However, we paid little attention to this condition at the time, for we felt that the psychic situation would clear up when the physical symptoms had disappeared.

At first, therefore, our endeavors were confined to explaining and treating the disorder on a purely physical basis. The most probable source of trouble at first was thought to lie in some one of the ductless glands. A therapeutic test was made with thyroid; but although the basal metabolic rate was raised to the normal level, little improvement was experienced by the patients. Indeed most of them were irritable and apprehensive in consequence of the treatment. Pituitary preparations were next tried, but without appreciable benefit. While these therapeutic tests were taking place, it was noted that the physical signs above referred to, were almost without exception the reverse of those described by Cannon¹ in his studies on the responses of animals to emotional stimuli and ascribed by him to generalized excitation of the sympathetic division of the autonomic nervous system. Throughout this paper, the division of the autonomic nervous system into sympathetic and parasympathetic is understood, as made by the pharmacologist rather than by the anatomist. The pharmacologist regards fibers stimulated by pilocarpine and paralyzed by atropine as parasympathetic; those stimulated by adrenalin as sympathetic. The anatomist regards fibers originating in the thoracic and lumbar regions of the cord, as sympathetic; in the brain stem and sacral region of the cord, as parasympathetic. A régime, therefore, was instituted to overcome this condition of autonomic imbalance. Cold baths, relatively small meals of easily digested food, moderate exercise and the use of drugs such as epinephrine, ephedrine and atropine were among the measures employed singly or collectively in the treatment of these

patients. There was no doubt that some of the patients were cured by these procedures, for the symptoms disappeared, the abnormalities revealed on physical examination or by the use of laboratory tests, were replaced by normal findings, and the patients expressed themselves as satisfied with the outcome. The results of treatment on laboratory manifestations are shown in Table 3.

TABLE 3.—RESULT OF PHYSICAL TREATMENT ON LABORATORY MANIFESTATIONS (8 CASES).

		(8 CASES).						
		Before treatment.			After treatment.			
1.	Blood pressure:							
	Maximum	108/70			124/80			
	Minimum	88/54			110/72			
	Mean*	96/64			114/72			
2.	Basal metabolic rate:							
	Maximum	- 2			+ 10			
	Minimum	- 22			- 4			
	Mean*	- 15			+ 3			
3.	Lymphocyte percentage:							
	Maximum	46			35			
	Minimum	34			28			
	Mean*	40			32			
Blood sugar tolerance:								
		30	60	90		30	60	90
	Fasting.	mins.	mins.	mins.	Fasting.	mins.	mins.	mins.
	Maximum	84	98	100	106	158	140	122
	Minimum	76	102	68	90	108	135	92
	Mean*	79	105	86	97	136	129	101

* The arithmetical mean of 8 cases.

In view of the fact that certain patients continued to have symptoms, although the physical signs and laboratory tests had reverted to normal following the institution of the régime mentioned above, it was decided to investigate further the rôle played by psychic factors. When this was done, it was quickly ascertained that patients very often complain of the physical symptoms of an emotional reaction, while they withhold the story of emotional strain. Basically, these patients showed a common psychic pattern. All were faced by situations which were disliked, which were intolerable, and which could not be altered. Indeed, each one rebelled against the established order of things in a matter which was, for him, unchangeable. In a measure, each one of them rebelled against himself or, at least, against the inevitability of his own limitations, for the attainment of every objective is conditioned by an individual's capacities. Where one recognizes that one's objectives are unattainable, wisdom, of course, demands that one's objectives be changed. Our patients were unfortunate in that they either could not or would not alter their objectives, even in spite of the fact that they realized the impossibility of attaining them. The task of psychotherapy was, therefore, to assist them to do this. In brief, our method of treatment consisted in a thorough mental catharsis for the patient (although not as complete as that employed by a psychoanalytic school) and then in assisting him to re-synthesize his experience so that he could, if he so chose, alter the objectives of his life. The results were so gratifying in the cases in which

it was used in conjunction with physical methods of treatment, that it was decided to try the effect of psychotherapy alone on patients with findings similar to those mentioned above. Our astonishment was great in learning that treatment of this type supplemented by no physical measures whatsoever, was followed by a disappearance of symptoms, a return of physical signs and laboratory tests to normal and a restoration of the patient to health both mental and physical. The results of treatment on the laboratory manifestations in patients of this group are given in Table 4.

TABLE 4.—RESULTS OF PSYCHOTHERAPY ON LABORATORY MANIFESTATIONS (20 CASES).

1. Blood pressure:								
Maximum	112/60		138/88	
Minimum	84/44		102/54	
Mean*	98/62		124/80	
2. Basal metabolic rate:								
Maximum	-3		+16	
Minimum	-21		-8	
Mean*	-11		+2	
3. Lymphocyte percentage:								
Maximum	53		39	
Minimum	33		28	
Mean*	41		29	
4. Blood sugar tolerance:								
	Fasting.	30 mins.	60 mins.	90 mins.	Fasting.	30 mins.	60 mins.	90 mins.
Maximum	90	160	132	108	96	164	128	90
Minimum	84	108	108	92	94	108	120	102
Mean*	81	110	121	106	99	131	116	113

* The arithmetical mean of 20 cases.

Comment. The observations recounted above lead naturally to many questions, to no one of which a final answer can be given at the present time. Some of these questions have proved to be particularly fascinating, and an effort will be made to suggest answers which fit in with the remainder of our present-day knowledge. What is the fundamental nature of the physical disturbance? Can this physical disturbance be produced by both physical and psychic causative factors? How can these observations be reconciled with those of Cannon in his studies on the emotional reactions in lower animals? Why is this symptom complex observed only in the young?

Light may be thrown on the answer to the first question by recounting the studies of the physiologist and pharmacologist. Indeed our first clue to the nature of the physical disturbance came when we noted that this was the reverse of that described by Cannon¹ in the lower animals. The physical disturbance in our patients was likewise the reverse of the change produced by adrenalin.² On the other hand, it was very similar to that produced by pilocarpine,² muscarine² and choline in the animal. While the two first named substances are not to be found in the body, choline and its esters are present there in at least small quantities. The action of this substance has been studied rather exhaustively by Hunt and Taveau,⁵ Dale,³ Feldberg and Gaddum,⁴ Loewi and Navratil,⁶ and it seems

to be productive of symptoms and signs qualitatively, although not quantitatively, similar to the symptoms and signs observed in our patients. The quantitative dissimilarity might be explained on the basis of the size of dose employed for physiological research. Accordingly, it seems reasonable to infer that our patients had symptoms and signs by reason of hyperactivity of the parasympathetic system or hypoactivity of the sympathetic system, or, to express it in another fashion, a predominant orientation towards the parasympathetic side in autonomic activity.

The second question proposed above cannot receive a final answer in the light of our present knowledge. Symptoms and signs similar to these are not uncommon in those convalescing from acute illness such as typhoid fever, lobar pneumonia and in those with wasting diseases such as pulmonary tuberculosis or carcinoma. Fatigue, large meals and hot baths likewise seem to favor a parasympathetic orientation of autonomic activities. In a sense, one can demonstrate all these things by a *a priori* experiment. To prove *a priori* that psychic factors can produce such symptoms and signs as observed in these patients is, however, quite impossible. Nevertheless, the effectiveness of psychotherapy in being followed by a disappearance of these symptoms and signs suggests that they were produced by psychic factors. Our series is too small to permit of generalization in this regard, but it does suggest that psychic factors can produce a predominantly parasympathetic orientation of the autonomic system.

The fact that Cannon has demonstrated by a *a priori* experiment a sympathetic hyperactivity in an animal which is emotionally stimulated at once casts doubt upon our hypothesis as to an emotional origin for the phenomena which we observed. A moment's reflection makes clear an important difference between man and the lower animals. Both can, of course, rebel against an undesirable environmental situation, but the lower animal in Cannon's experiments rebelled against situations the menace of which might be overcome by the full utilization of his bodily resources, whereas man can, and oftentimes does, rebel not only against situations which can be overcome by his limited power but also against situations which he cannot overcome at all. Furthermore, man's rebellion against the inevitable and the unchangeable may be not the matter of a moment but the matter of days, of months, or of years. Analogous situations cannot be produced in a laboratory. It is, of course, true that one can observe in man the condition of hyperactivity of the sympathetic system, which is brought about by emotional factors, but in such cases the menacing influence is one which presumably can be overcome by the employment of all the bodily resources at man's disposal. These resources are mobilized through the activity of the sympathetic system. However, when man is faced by a menace which he cannot overcome (and menacing influences of this type confronted the patients discussed above), there

seems little utility in mobilizing the body's resources for such a contest. In such cases, hypoactivity of the sympathetic system, hyperactivity of the parasympathetic system, or a combination of both does not seem unreasonable to expect. In view of these considerations it is our belief, although our data is insufficient to prove this beyond reasonable doubt, that emotional situations brought about by a menace which is regarded as capable of being overcome is followed by predominantly sympathetic orientation of the autonomic system, but that emotional disturbances brought about by an insuperable menace are followed by predominantly parasympathetic orientation.

That these congeries of signs and symptoms have been observed only in the young does not seem particularly remarkable, when one considers that the mature oftentimes have irreversible changes in tissues as the concomitant of age. Irreversible changes would necessarily modify any symptom complex. Furthermore, a functional system complex, if prolonged, might be expected to result itself in irreversible anatomic change.

Summary. The symptoms, physical signs and laboratory data found in 20 patients, diagnosed as psychoneurotics, because of the absence of demonstrable physical disease and because of the effectiveness of psychotherapy in bringing about a cure, are reported as found before and after treatment. The symptoms, physical signs and laboratory data are similar to those which one would expect from stimulating the parasympathetic division of the autonomic nervous system.

The difficulties of employing the *a priori* scientific method in psychosomatic research are enumerated, in explanation of the fact that the conclusions in this paper are mostly obtained by *a posteriori* reasoning.

It is suggested that menacing influences which may be surmounted give rise to an emotion in which the predominant physical manifestations are due to stimulation of the sympathetic division of the autonomic nervous system; and that those which appear insurmountable give rise to an emotion in which the predominant physical manifestations are due to stimulation of the parasympathetic division of the autonomic nervous system.

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BOOK REVIEWS AND NOTICES.

ORAL HYGIENE AND THE TREATMENT OF PARODONTAL DISEASES. By RUSSELL W. BUNTING, D.D.Sc., Professor of Oral Histology and Pathology in the School of Dentistry of the University of Michigan, Ann Arbor. Pp. 187; 80 illustrations. Philadelphia: Lea & Febiger, 1936. Price, \$2.50.

AFTER many years of experience, the author has presented this book for the use of students and practitioners of the dental profession in the sincere belief that mouth hygiene must be more thoroughly understood if the practice of dentistry is to fulfill its true purpose. The aim of this book is to indicate to practitioners in general that mouth health cannot be separated from general health.

The first section deals with oral hygiene proper and the salient features of oral sepsis, the prevention of dental caries, the prevention of parodontal infections and oral prophylaxis. The second section is devoted to an extensive discussion of parodontal diseases and their treatment. Gingivitis, parodontitis, pericemental abscess, Vincent's infection and gingival atrophy are presented in a comprehensive fashion. Facts are not merely presented but interpreted and explained.

The author has taken great care to select and review outstanding beliefs concerning the maladies discussed and to stress just those points which are interesting and important to know.

This is a book that might profitably be used by student, the practitioner and all those interested in Oral Hygiene and the relation of mouth sepsis to systemic diseases.

T. C.

A TEXT-BOOK OF PATHOLOGY. By W. G. MACCALLUM, Professor of Pathology and Bacteriology, The Johns Hopkins University, Baltimore. Pp. 1277; 697 illustrations. Sixth Edition, entirely reset. Philadelphia: W. B. Saunders Company, 1936. Price, \$10.00.

THE long continued and wide use of this text-book of pathology is an indication of its excellence. The new edition follows the previous system of arrangement of material on an etiological basis, rather than the arrangement usual in other text-books according to organs and systems. Two chapters on infections of uncertain nature, in the previous edition have been reclassified as a chapter on rickettsia infections and five chapters on filterable viruses. Rheumatism has been dealt with under the latter category because the author considers that "it seems probable that rheumatism is caused by one of those elusive filterable infective agents," although he gives no positive evidence to support this. This is a radical departure from the current concept of this disease. Equally surprising in his inclusion of scarlet fever as a virus disease, and of periarteritis nodosa as apparently a virus infection. This illustrates the difficulties of treating pathology on an etiological basis, and this system requires a discriminating reader. New chapters deal with fungus infections; with diseases of the central nervous system of unknown etiology; with teeth and related structures; and with congenital malformations. Injuries to organs of internal secretion now constitute six chapters instead of the former three. Many new illustrations from the author's own material are excellent, and as in previous editions, descriptions of pathological processes drawn from the author's personal experience are effective.

I. Z.

AN INTRODUCTION TO MATERIA MEDICA AND PHARMACOLOGY. By HUGH ALISTER McGUIGAN, Ph.D., M.D., Professor of Materia Medica, Pharmacology, and Therapeutics, University of Illinois, College of Medicine, Chicago, and EDITH P. BRODIE, A.B., R.N., formerly Director School of Nursing, Vanderbilt University, Nashville; formerly Instructor in Materia Medica and Therapeutics, Washington University School of Nursing, St. Louis. Pp. 580; 71 illustrations and 18 color plates. St. Louis: The C. V. Mosby Company, 1936. Price, \$2.75.

THE preface states that "this book is the outgrowth of an attempt to revise the Fourth Edition of Brodie's *Materia Medica for Nurses*." The rising standards of the nursing profession are depicted in the scope and nature of this work. It contains a brief but well-done history of drug-giving. The chemical nature of drugs is shown by means of structural formulas; experiments illustrating various features in the action of drugs are described and numerous records are given. There is more direct correlation with bedside therapeutics and greater attention to the preparation and administration of drugs than is usual in books on pharmacology for medical students; controversial points are also treated briefly, and properly so in view of the purpose of the book. The only adverse criticism the reviewer can make against this work is that it may be too difficult for the average nurse. Certainly it affords an opportunity for acquainting student nurses with the facts of modern pharmacology and deserves serious consideration by those upon whom that task devolves.

C. S.

DIGESTION AND HEALTH. By WALTER B. CANNON, George Higginson Professor of Physiology, Harvard Medical School. Pp. 160; 14 illustrations. New York: W. W. Norton & Co., Inc., 1936. Price, \$2.00.

IN this small volume Dr. Cannon has described for the lay reader the nature of hunger and of thirst and has described the mechanism of autonomic control of gastro-intestinal function and the influence of emotion upon this control. In the exposition of his material Dr. Cannon has described in simple terms the classical experiments in these fields, including in certain instances graphs and figures from the original articles. He has thus allowed the lay reader to see the way in which scientific facts are accumulated. This method of presenting the subject-matter may be a little difficult for some readers to follow, but from the information so presented practical applications are indicated which should be understandable and of interest to the thoughtful layman.

K. E.

THE CLINICAL USE OF DIGITALIS. By DREW LUTEN, A.B., M.D., Associate Professor of Clinical Medicine in the Washington University School of Medicine and Physician to Barnes Hospital, St. Louis. Pp. 226; 5 illustrations. Springfield, Ill.: Charles C Thomas, 1936. Price, \$3.50.

A CONCISE, yet inclusive, discussion of digitalis therapy. The first portion of the book emphasizes important pharmacologic concepts. Then follow chapters on indications and contraindications; dosage and methods of administration; and the prognostic value of the response to digitalis. The final chapter, entitled Therapeutic Theses, is a group of summarizing aphorisms.

The author uses the historical approach effectively, to support the rationale of his arguments. The style is readable and emphatic. Some might criticize the omission of a rule-of-thumb outline for digitalis dosage. Most readers, however, will agree with the author's viewpoint when he refuses to do so.

W. J.

A DISSERTATION ON THE SENSIBLE AND IRRITABLE PARTS OF ANIMALS. By ALBRECHT VON HALLER [London, J. Nourse, 1735]. Introduction by OWSEI TEMKIN. Pp. 49; 1 illustration. Baltimore: The Johns Hopkins Press, 1936. Price, \$1.00.

THIS reprint of an anonymous English translation of Haller's celebrated work is welcome both as an easily available form of an important physiological treatise and also, as Temkin points out in his introduction, as "an outstanding document of indefatigable experimentation and clear reasoning." Though the phenomena of sensibility and irritability (a term coined by Glisson) were recognized long before Haller, to him is due the credit for recognizing their independence and the clear distinctions between them. His line of reasoning is interesting to follow. E. K.

THE RIDDLE OF WOMAN. A Study in the Social Psychology of Sex. By JOSEPH TENENBAUM, M.D., Director of Urological Service in the Central Neurological Hospital, Welfare Island. Pp. 477. New York: Lee Furman, Inc., 1936. Price, \$3.50.

IN title, this book is designed for popular appeal and the approach to the subject-matter so definitely Freudian, that it will find but small favor with most physicians. Some of the angles from which Woman is discussed, are: A Social Problem, The Sex Urge in Woman, The Wife, The Bride, The Adultress, The Virgin, The Spinster, The Witch, The Beautiful Woman and The Prostitute. Freud is the author most frequently quoted together with "Albert Einstein, the greatest genius of the age." A vast amount of data are assembled and the "Riddle" is not solved. N. Y.

CHEMICAL PROCEDURES FOR CLINICAL LABORATORIES. By MARJORIE R. MATTICE, A.B., SC.M., Assistant Professor of Clinical Pathology, New York Post-Graduate Medical School of Columbia University; Assistant Director of the Biochemical Laboratory, New York Post-Graduate Hospital; Consultant Chemist, Reconstruction Hospital, New York City. Pp. 520; 90 illustrations and 2 colored plates. Philadelphia: Lea & Febiger, 1936. Price, \$6.50.

THE author has organized a wealth of trustworthy procedures and valuable information into four groups:

Part I. Blood. Following a preliminary discussion of the functions and general properties of blood are given reliable procedures for determining the acid-base balance of the blood, carbohydrates and ketones, cholesterol and other lipids, plasma proteins, non-protein nitrogen and its components, hemoglobin, serum pigments and hepatic function tests, and inorganic constituents. The subject matter is extremely well organized and the tests are standard.

Part II. Clinical laboratory procedures of urine testing are presented in the same way as is the blood in Part I. It is quite thorough.

Part III. Gastro-intestinal Secretions. This is a trustworthy and gratifying section. The Lueder-Hollander System for estimating the duodenal enzymes is given.

Part IV. In this section is included both qualitative and quantitative methods of examination of miscellaneous biological fluids, such as milk, cerebrospinal fluid, and effusions.

Scattered through the text are practical discussions dealing with sources of error and methods of eliminating them. The interpretations are conservative yet thorough. This book is not to supplant standard texts of physiologic chemistry as its greatest use will be to clinical pathologists and their assistants. Every clinical laboratory should have a copy. J. B.

MEDICAL CLASSICS. Volume 1, No. 1 (September, 1936) (Ten issues a year). Compiled by EMERSON CROSBY KELLY, M.D., of the Department of Surgery, Albany Medical College. Pp. 78; illustrated. Baltimore: The Williams & Wilkins Company, 1936. Price, \$10.00 per volume.

THE desirable vogue of reprinting important medical articles so that they are more easily available to the historically minded reader has further support in this new series of Medical Classics. In periodical form, more elastic and extensible than the books of this kind that have hitherto appeared, this venture need only be limited by the success of its reception. Let us hope that this will be conspicuous and that the series will have a long and useful career in stimulating the medico's interest in the historical side of his profession. This first number reproduces in their complete original form three of Paget's most important contributions. Who is there who will disagree with the compiler's view that "every doctor who has a patient with osteitis deformans or one in whom osteitis deformans is a possibility will be a better doctor if he knows intimately the writings of Paget on this subject?" And for that matter, even if he has not such a patient, will he not be a better doctor and one better satisfied with his profession, if he reads these brilliant descriptions and begins the habit, if he has not already formed it, of going back to the masters' original descriptions? Not the least useful in this number, is a bibliography of 175 medical articles by Paget. We should welcome most heartily this latest addition to the armamentarium that brings the high spots of medical history the more easily to our aid.

E. K.

OPERATIVE AND INTERPRETIVE RADIODONTIA. A Textbook for Students and Practitioners of Dentistry. By WALTER S. THOMPSON, D.D.S., Associate Professor of Radiodontia, College of Dentistry, University of Southern California; Lieutenant, U. S. N. R., Special Service Instructor in Radiodontia, etc. Pp. 374; 355 illustrations. Philadelphia: Lea & Febiger, 1936. Price, \$7.00.

THIS volume is a concise and comprehensive presentation of roentgenology as applied to dentistry, written in an attractive and readable style. The first part deals with operative radiodontia in which there is introduced the history of radiodontia, followed by the physics of Roentgen rays, with a consideration of the mechanical appliances employed in radiodontia, the technique of dental roentgenology and the processing of dental films. Particularly commendable is the chapter devoted to the biological effects of Roentgen rays, in which special emphasis is placed on the danger inherent in their use. Important is the consideration given to the roentgenological aspects of the structures in the proximity of the dental arches, such as the maxillary sinuses and the salivary glands. The technique for the use of diagnostic-radiopaques is included. Many special procedures to be used in the occasional case are described. The text is amply and beautifully illustrated.

Interpretative radiodontia is dealt with in considerable detail. This is introduced by a consideration of Roentgen ray absorption and followed by interpretative studies based on dental anatomy and pathology. The closing chapter on radiation therapy indicates that this work is quite modern in every respect. The author rightfully infers that radiation therapy is a fruitful field for future researches in dentistry.

This volume will have a wide appeal, not alone for students and practitioners of dentistry, for whom it will serve as an excellent text and reference work, but also for the general roentgenologist, who is required to possess considerable knowledge of radiodontia.

K. K.

DIE NEBENNIERENRINDE. Beiträge zur Experimentellen und Klinischen Pathologie. By DR. MED. SIGISMUND THADDEA, Assistent der II. Med. Universitätsklinik der Charité, Berlin. Pp. 199; 78 illustrations and 36 tables. Leipzig: Georg Thieme, 1936. Price: Paper, M. 11.; Bound, M. 13.

THIS book is essentially a rather extensive review of the literature and the author's own experiments concerning the adrenal cortex. Emphasis is placed upon the metabolic and physiologic aspects. Historical and morphological considerations and details as to preparations of active extracts are but briefly discussed.

The main sections deal with muscle weakness, growth, temperature, water, mineral, blood, circulation and respiratory changes, and most thoroughly with metabolism. Especially interesting are the author's experiments concerning carbohydrate and cholesterol metabolism. Unfortunately his experiments are not given in detail; many simply confirm previous work. In the majority of experiments reported no mention is made as to whether or not salt was used.

The last portion is devoted to Addison's disease, adrenal cortical hormone therapy and relationship of the adrenal cortex to the other endocrine glands and to the vitamins. The book is succinct and well organized, having numerous subheadings. There are no descriptions of technique. It may be recommended to those interested in endocrine or metabolic problems.

C. D.

LANE MEDICAL LECTURES: STUDIES IN CARDIOVASCULAR REGULATION. By G. V. ANREP, M.D., D. Sc., F.R.S., Professor of Physiology, Medical Faculty, Egyptian University, Cairo, Egypt. Pp. 118; 38 figures and 8 tables. Stanford University, Calif.: Stanford University Press, 1936. Price: Paper, \$1.50; Cloth, \$2.25.

THE five lectures contained in this book deal with 1, The Proprioceptive Mechanism of Cardiovascular Regulation; 2, The Respiratory Regulation of the Heart Rate; 3, The Dynamics of the Coronary Circulation; 4, The Coronary Blood Flow and 5, The Blood Flow Through Skeletal and Plain Muscles.

The author, in addition to being a distinguished investigator in the field of circulatory physiology, proves himself to be an excellent interpreter of the highly technical literature of the subject. The lectures are couched in simple language and the thought is easy to follow. This little volume is highly recommended to all who wish to keep track of what the physiologists are accomplishing by their researches on the circulation.

C. W.

A PRACTICAL MEDICAL DICTIONARY. By THOMAS LATHROP STEDMAN, A.M., M.D. Pp. 1282; illustrated. Thirteenth Edition, revised with the New British Anatomical Nomenclature (9 pages). Baltimore: William Wood & Co., 1936. Price, \$7.50 with thumb index; \$7.00 without.

ALWAYS one of our best medical dictionaries, with the advantage of 25 years under the same editor, this work appears in a new edition that has included hundreds of new terms and various changes that put it in accord with the 1936 U. S. Pharmacopoeia. Especially interesting to the Reviewer are the initial pages from the Eleventh Edition Preface and on Medical Etymology, wherein are given rules and examples of proper spelling and the history of the editor's successful struggle to extinguish errors (such as improper omission of the final e, change of k for c, etc.) that had been promoted in other quarters.

E. K.

PSYCHIATRY FOR PRACTITIONERS. [Reprinted from Oxford Loose-Leaf Medicine.] By various authors. Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (HON.); Hersey Professor of the Theory and Practice of Physics, Harvard University; Physician-in-Chief to the Peter Bent Brigham Hospital, Boston. Pp. 646. New York: Oxford University Press, 1936. Price, \$6.50.

THIS reprint from Oxford Loose-Leaf Medicine is by 11 collaborators. E. A. Strecker and H. D. Palmer contribute the recognition and management of the beginning of mental disease; Gerald Pearson, psychiatry of childhood; Earl D. Bond, post-encephalitic and post-traumatic behavior disorders; E. A. Whitney, mental deficiency; Eugen Kahn, psychopathic personalities; F. G. Ebaugh, toxic reaction types; W. A. White, paranoia and paranoid conditions; C. O. Cheney, dementia præcox (schizophrenia) group; D. K. Henderson, affective reaction type (manic-depressive) including involuntional melancholia; T. A. Ross, psychoneuroses.

Toxic reaction types is an excellent chapter and since the induction of malaria in the treatment of paresis is so admirably considered, it need not have been described elsewhere. Chapters on affective reaction types and psychoneuroses are worthy of special mention. Too many historic characters are classed as epileptics, *e. g.*, Byron, Peter the Great and Napoleon. Once when Kean was acting, many in the audience were overcome and Byron fell into a fit which appeared to be hysterical; his feet were deformed but not from a central lesion—they were club-feet. As to Peter the Great and Napoleon, each was a *tiqueur*; the latter, after long hours of work would at times show a tic—frequent and rapid elevation of the right shoulder—which to those unfamiliar, was sometimes mistaken for a gesture of disapproval. The terms "Post-traumatic neuroses" and "psychoses" should be written with the "post." The book serves its purpose well, but it is hoped a subsequent edition will contain a more complete index. A glossary would aid general practitioners greatly. N. Y.

A TEXTBOOK OF SURGERY. By JOHN HOMANS, M.D., Clinical Professor of Surgery. Compiled from Lectures and Other Writings of 23 Members of the Surgical Department of The Harvard Medical School. With a Special Bibliographical Index and illustrations by Willard C. Shepard. Pp. 1267; 530 illustrations, Fourth Edition. Springfield, Ill.: Charles C Thomas, 1936. Price, \$8.00.

THE appearance of this work so quickly in its Fourth Edition demonstrates that it has met the needs of the professional public in this particular branch—surgery. The book is an extremely popular one for students, practitioners and specialists alike. It covers the field completely and sufficiently thoroughly to satisfy the needs of its readers. This edition has been entirely re-written as well as re-edited; all old material has been replaced with new and there has been added a chapter on Amputations and Plastics. Revision has taken into consideration such subjects as Antiseptics and Sterilization, the Sympathetic Nervous System and the Thyroid Gland. Much valuable information has been added with regard to certain fractures, yet, with all of these additions the size of the volume has not been materially changed.

Recognizing the fact that it is an extremely difficult problem to write a one volume surgery to meet all needs, the Reviewer thinks that this particular work fulfills the aim as near as possible under the present conditions.

The subject matter is covered in a sufficiently comprehensive manner to fit practically all requirements. The book is all that is necessary for the student and at the same time has sufficient reference value to be a handy work for the specialist. E. E.

PRINCIPLES OF BIOCHEMISTRY. By ALBERT P. MATHEWS, Carnegie Professor of Biochemistry, University of Cincinnati, Cincinnati, Ohio. Pp. 512; 3 illustrations. Baltimore: William Wood & Co., 1936. Price, \$4.50.

THIS book is presented as a completely new and rewritten textbook for students of medicine and is not to be regarded in any sense as a revision of Dr. Mathews' older and formerly widely used textbook on Physiological Chemistry.

In his preface the author sets up as one aim the presentation of the subject in such way that it "will appear, not as an inchoate assembly of facts, but as making part of a great science which reveals the finer structure and coördinated chemistry of the human body." In this laudable attempt, Dr. Mathews has not, in the opinion of this Reviewer, been uniformly successful. One often feels, in reading the book, that unfortunately little discrimination has been used between topics of prime physiological importance and others that hardly merits any space whatever. This produces an effect of giving a large mass of uncorrelated information, important and unimportant, with very little critique to guide the student.

For example, the general topic of acid-base balance as reflected in both blood and urine is given very scanty attention; and on page 373, in discussing acid-base balance two paragraphs of equal length deal, respectively, with the effects of various foods on the alkalinity of the urine and with the effect of cancer and other conditions on the pH of blood. It would seem that the effect of various foods on acid-base balance would far outweigh, in importance, a topic so controversial and so little substantiated as the effect of cancer on blood pH. Other examples of such unbalanced treatment could be mentioned.

Part V, dealing with the vitamins and hormones appears to be a very valuable part of the book. The author's treatment of these topics is full and as nearly up-to-date as could be expected in so active a field.

The book is compact, well arranged and is written for the most part in Dr. Mathews characteristically interesting style. J. A.

THE GIFT OF COLUMBUS. By CHARLES C. DENNIE, M.D., Kansas City, Mo. Pp. 195. Kansas City, Mo.: Brown-White Co., 1936. Price, \$2.00.

THIS book has been prepared for those who have not yet acquired syphilis, but who may do so. In general, it takes a sound attitude toward the proper ways of sociologically combating the spread of the disease and of medically treating those unfortunate enough to have acquired it. It is particularly appropriate at this time, when Surgeon General Parran is so efficiently bringing the fight against "the social disease"—a euphemism used more than once even in this book—out into the open. All the more disappointing is it then, to be unavoidably struck by the book's shortcomings. The title has novelty, to be sure, as the author uses it to mean that Columbus' crew brought syphilis to the West Indian natives! But why ignore the mass of evidence to show that syphilis existed in the Western World before Columbus? Typographical errors ("agrecake," "high domed literatuers," etc.) vie with questionable or incorrect statements ("95% of those so afflicted [aortic regurgitation and aortitis] have to thank syphilis"); while the company of mis-spelled worthies is indeed a motley one (for instance, "Lazarus Reverius, Oveido, Fornier, Montego, Wasserman, Erlich, Laewenboeck, Jonothan Hutchinson, Colle"). Even a book for popular consumption, deserves greater accuracy than this. E. K.

BRITISH MASTERS OF MEDICINE. Edited by SIR D'ARCY POWER, K.B.E., F.R.C.S., F.S.A., Consulting Surgeon and Archivist to St. Bartholomew's Hospital; Honorary Librarian, Royal College of Surgeons of England. Pp. 242; illustrated. Baltimore: William Wood & Co., 1936. Price, \$3.00.

INTERMEDIATE in size between the short notes of a biographical dictionary and the monographs that are necessarily restricted to the more famous, these 24 articles give us a pleasant picture of British medicine from Harvey to Starling, together with sympathetic personal sketches, each with portrait, "written by those who have been attached to the great institutions which their heroes made famous." While obviously accounts of Sydenham, Hunter, Lister and others of that ilk can easily be found elsewhere, a new interpretation may always be interesting; and for such as Floyer, Willan, William Ferguson, R. B. Todd, one might have to make a considerable search for an equally satisfying presentation. The moderns included are William Turner, Owen Thomas, Robert Jones, Manson, Osler, Mackenzie, Starling. The articles are reprinted from the pages of the *Medical Press and Circular*; the initials of the author of each sketch are found in a list following the List of Illustrations.

E. K.

ATLAS OF CONGENITAL CARDIAC DISEASE. By MAUDE E. ABBOTT, B.A., M.D., F.R.C.P. (CANADA), Curator of the Historical Medical Museum and Assistant Professor of Medical Research, McGill University, Montreal, Canada. Foreword by DR. PAUL D. WHITE. Pp. 72; 25 plates with more than 200 illustrations. New York: American Heart Association, 1936. Price, \$5.50.

MAUDE ABBOTT writes with recognized authority on the subject of Congenital Heart Disease, and anything that emanates from her pen needs no laudatory introduction nor recommendation. Her new Atlas of Congenital Cardiac Disease, however, is particularly worthy of praise. For those readers who feel they have neither the special interest nor the time to read her monographs, this all-too-short atlas uniquely fills a gap in essential clinical knowledge.

Part I deals with the development and comparative anatomy of the heart. Part II presents the clinical classification of Congenital Cardiac Disease. The atlas is replete with case presentations and clinical features, diagrams, illustrations of specimens, roentgenograms, electrocardiograms and a full bibliography. A valuable addition is the statistical table of 1000 analyzed cases. This excellent atlas serves to whet an already impatient appetite for the larger volume on Congenital Cardiac Disease which the author is preparing.

A. M.

RECENT ADVANCES IN ALLERGY. (Asthma, Hay-Fever, Eczema, Migraine, etc.). By GEORGE W. BRAY, M.B., CH.M. (SYDNEY), M.R.C.P. (LONDON), Physician in Charge of Children's Department, Prince of Wales Hospital; Assistant Physician, Princess Elizabeth of York Hospital for Children, etc. With Foreword by ARTHUR F. HURST, M.A., M.D. (OXON.), F.R.C.P., Senior Physician, Guy's Hospital, etc. Pp. 517; 107 illustrations, including 4 colored plates. Third Edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, \$5.00.

WITH 13 additional pages of text and some 2000 references to the literature, the new edition of this excellent work is highly recommended to students and practitioners as a well-rounded treatise on allergy. Its only disadvantage from the American standpoint continues to be the lack of hay fever plant surveys for this country.

R. K.

ATLAS OF HUMAN ANATOMY, with Explanatory Text. By **JESSE FEIRING WILLIAMS, M.D.**, Columbia University. Colored illustrations by **Franz Frohse**, University of Berlin, and **Max Brödel** and **Leon Schlossberg**, of Johns Hopkins University. Pp. 64. New York: Barnes & Noble, Inc., 1935. Price, Paper, \$1.25; Cloth, \$2.00.

This book, "designed for both the layman and the student of anatomy," contains a surprisingly large amount of information in a small space. Also the names of the illustrators are sufficient guarantee for the accuracy of the beautiful drawings. Yet with its brief text it is far from a substitute for a standard textbook for the medical student—probably was not so intended—and should only serve the medical man in such ways as when he wishes to demonstrate to his patient.

E. K.

TREATMENT IN PSYCHIATRY. By **OSKAR DIETHELM, M.D.**, Professor of Psychiatry, Cornell University Medical College, New York; Psychiatrist-in-Chief, the New York Hospital (Payne Whitney Psychiatric Clinic), etc. Pp. 476. New York: The Macmillan Company, 1936. Price, \$4.00.

MUCH reverence is shown herein to the author's former master, Adolf Meyer, whose psychobiology, "the hypothesis that matter and its functions belong inseparably together, forming a unit . . . and known as the principle of integration," threads its way through the book. Important chapters are: study of personality; suggestion and hypnosis; psychoanalytic procedure; excitements; depressions; schizophrenic reactions; paranoid and paranoiac reactions; psychoneuroses; stuttering, tics, occupational reactions and psychopathic personalities.

Psychoanalysis as expounded by Freud, Adler, Jung and others, is given; and Kronfeld's "psychagogy," scientific re-education that does not tend to be exclusively individualistic, is described. It is stated Meyer coined the term, "mental hygiene," but Sweetser, in 1850, wrote a volume bearing the title. The book under review, with 45 case reports, contains new and useful information, but a more systematic arrangement would add to its usefulness. The chapter on depressions consists of 32 pages with no subdivisions, and in the index nothing pertinent follows depressions that would direct attention to any of its details.

N. Y.

ON THE DISTURBANCE OF THE CIRCULATION IN SPINAL ANESTHESIA. An Experimental Study. By **OSCAR O. SCHUBERTH**. Pp. 77; 2 illustrations and 30 tables. Stockholm: P. A. Norstedt & Sons, 1936. (Price not given.)

THIS little monograph records the data and conclusions of Schubertsh after an exhaustive study of the dynamic disturbances of the circulation in experimental spinal anesthesia. In the major portion of the work the experimental investigations were done on animals but limited observations were made on man. There is an introduction and two major subdivisions. The one, "The influence of spinal anesthesia on certain circulatory factors," considers oxygen consumption, arteriovenous oxygen difference, cardiac output, venous pressure, the blood volume and the capillary picture. The second deals with the influence on respiration of spinal anesthesia, involving the dorsal, but not the cervical cord. Each section consists of a short survey of previous investigations and these are followed by the author's data and discussion. The author concludes that the shocklike state which may accompany spinal anesthesia is different from most other types of shock in that there is no decrease in the circulating blood volume. This monograph is the best that the Reviewer has seen on the subject. There is a summary and an excellent bibliography.

L. R.

DISEASES OF THE CORONARY ARTERIES AND CARDIAC PAIN. Edited by ROBERT L. LEVY, M.D., Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University; Associate Visiting Physician and Cardiologist, Prebyterian Hospital, New York City. Advisory Editorial Committee: ALFRED E. COHN, JAMES B. HERRICK, CARL J. WIGGERS; 14 Contributors. Pp. 445; 97 illustrations. New York: The Macmillan Company, 1936. Price, \$6.00.

Few branches of medicine have made more progress in this century than has the knowledge of cardiovascular disease, and no branch of cardiovascular study has progressed more in the past 20 years than has the study of the coronary arteries. Establishment of the criteria for recognizing coronary occlusion by James Herrick—one of the contributors to this volume—not only was of prime importance on its own account but apparently initiated fruitful studies in the anatomy, physiology and pathology of this vital part of the arterial tree. These studies have formed the core about which 14 of the leading students of coronary disease in this country have collected 17 chapters on the nature of coronary disease, its recognition and frequency and its medical and surgical treatment. Physicians, surgeons and their preclinical colleagues all should find this a timely, interesting and valuable—for many, invaluable—book.

LECTURES ON EMBOLISM AND OTHER SURGICAL SUBJECTS. (The Abraham Flexner Lectures, Series No. 4.) By GUNNAR NYSTROM, M.D., Professor of Surgery, University of Uppsala, Sweden; Chief of the Surgical Clinic and Director of the University Hospital, Uppsala. Pp. 213; 22 illustrations. Baltimore: Williams & Wilkins Company, 1936. Price, \$3.00.

This interesting little volume contains 5 chapters representing 5 formal lectures given by Professor Nystrom at Vanderbilt University. The first is on "Embolism of the Arteries of the Extremities and Its Treatment," the second on "Pulmonary Embolism and Its Surgical Treatment," the third, "Swedish Experiences in Combating Appendicitis," the fourth, "The Cytology of Joint Exudates as an Aid to Diagnosis," the fifth, "The Treatment of Medical Fractures of the Collum Femoris." The chapters on embolism are fascinating and all full of advice on diagnosis and treatment. In this field the Scandinavian surgeons have played the most important rôle. The lecture on appendicitis the treatment of this common surgical lesion serves to portray the general nature of the practice of surgery in Sweden. The lecture on the cytology of joint exudates adds an interesting chapter to our knowledge of the cytology of effusions of the pleura and peritoneum. In the chapter on fractures of the neck of the femur the author pays high tribute to the work of American surgeons in this field. The lectures are simply but well illustrated and considerable statistical data are included in numerous tables. The volume forms a welcome addition to the surgical essays which have recently been published in this country.

THE PHYSIOLOGY AND PHARMACOLOGY OF THE PITUITARY BODY. By H. B. VAN DYKE, Professor of Pharmacology, Peiping Union Medical College, Peiping, China. Pp. 577; 55 illustrations. Chicago: The University of Chicago Press, 1936. Price, \$4.50.

This is an excellent review of the voluminous literature on the pituitary. The bibliography alone covers 181 pages. The data described are well systematized, so that one can look up desired points with ease. The 55 illustrations are exceedingly well selected. We believe that this will be a valuable aid to students and investigators in this field.

I. R.

I. Z.

THE PRINCIPLES OF BACTERIOLOGY AND IMMUNITY. By W. W. C. TOPLEY, M.A., M.D., M.Sc., F.R.C.P., F.R.S., Professor of Bacteriology and Immunology, University of London; Director of the Division of Bacteriology and Immunology, London School of Hygiene and Tropical Medicine, and G. S. WILSON, M.D., F.R.C.P., D.P.H., Professor of Bacteriology and Applied Hygiene, University of London, London School of Hygiene and Tropical Medicine. Pp. 1645; 276 illustrations and 192 tables. Second Edition. Baltimore: William Wood & Co., 1936. Price, \$12.00.

It is not surprising that such an actively progressive subject as bacteriology should require new presentations at frequent intervals. This book, acclaimed as a leader shortly after its first appearance in 1929, retains its premier position in its new form. Admittedly more comprehensive than the average textbook for medical students, it has been found in at least one of our medical schools to be the most desirable to put in the student's hands, with recommendations for selective topical reading. Thus properly used, the wealth of detail constitutes an asset for a reference book, without harming its value as a students text. The extensive alterations that new concepts and facts have required have not changed the original plan or arrangement nor greatly increased the book's size. E. K.

THE LUNG. By WILLIAM SNOW MILLER, Emeritus Professor of Anatomy, University of Wisconsin. Pp. 209; 152 illustrations, including 20 colored plates. Springfield, Ill.: Charles C Thomas, 1937. Price, \$7.50.

THIS is a monograph on the structure—especially the microscopic structure—of the lung. Its greatest value lies in its superb illustrations, because these enable the reader to grasp and understand pulmonary structure in three dimensions. The two dimensional pictures familiar to the microscopist is a very different thing, and scarcely gives an inkling of the relations of respiratory bronchioles, atria, air sacs and alveoli as reconstructed by Dr. Miller from serial sections. Besides the section on the anatomy of the air passages, there are chapters on blood vessels—the richness of the capillary network is astonishing—the lymph nodes, lymphoid tissue, nerves and pleura. A remarkable feature is a well-illustrated chapter on the structure of the lung as conceived by other anatomists from Malpighi to the present time.

With Dr. Miller's conclusions on such controversial subjects as the epithelial lining of the alveoli and the presence or absence of alveolar pores, the reader may or may not agree. But all sides of these questions are covered by citations from the literature, and the author's own position is supported by good evidence.

In conclusion, this book deserves to commend a notably fine example of book making. M. McC.

BAILEY'S TEXT-BOOK OF HISTOLOGY. (Elwyn and Strong.) By PHILIP E. SMITH, Professor of Anatomy, Editor, RUSSELL L. CARPENTER, Ph.D., WILFRED M. COPENHAVER, Ph.D., CHARLES M. GOSS, M.D., AURA E. SEVERINGHAUS, Ph.D., all Assistant Professors of Anatomy, College of Physicians and Surgeons, Columbia University. Pp. 773; 506 illustrations, some in colors. Ninth Edition, revised and rewritten. Baltimore: William Wood & Co., 1936. Price, \$6.00.

IN this edition all chapters but one have been changed and four have been rewritten—so great is the progress in even such a static subject as normal histology. The work continues to be primarily for medical students though "major controversial differences of opinion" have been included. The editors continue to emphasize that "structure assumes its full meaning only when correlated with function." E. K.

THE DEVELOPMENT OF MODERN MEDICINE. An Interpretation of the Social and Scientific Factors Involved. By RICHARD HARRISON SHRYOCK, Professor of History, Duke University. Pp. 442; illustrated. Philadelphia: University of Pennsylvania Press; London: Oxford University Press, 1936. Price, \$4.00.

MEDICAL historians have become increasingly aware of the need of considering their field as but a branch of the history of science, and this, in turn, of the history of the world. The story is necessarily fragmentary if these backgrounds are not given their due position. Conversely, the general historian should find the art and science of medicine a desirable field of study, and yet how seldom does he invade it and how often is medical history written by those untrained historically! This attempt, then, by a professional historian "to portray certain major aspects of medical development against the background of intellectual and social history in general" has an added value in closing a long open gap. Those physicians who are at all historically minded will not be surprised at the general conclusion drawn; namely, that measurement, experiment and the use of instruments have been chiefly responsible for the advance of medical science; yet he probably will be surprised, and certainly should have his curiosity aroused, by the emphasis laid on such discussions as the failure of physical science in the 18th century, the social factors concerned in the medical lag, the loss of the public's confidence in the early 19th century, and its reacquisition at the end of the same century.

In this book the reader will find little about the outstanding men of our profession and nothing about the medicine of antiquity or of barbarous countries; but he will find an accurate, logical consideration of modern medical developments, traced from an unusual point of view, which should give him a better background for 20th century problems of medicine than does the conventional history of medicine. E. K.

SKIN DISEASES IN CHILDREN. By GEORGE M. MACKEE, M.D., Professor of Clinical Dermatology and Syphilology, New York Post-Graduate Medical School, Columbia University, and ANTHONY C. CIPALLARO, M.D., Associate in Dermatology and Syphilology, New York Post-Graduate Medical School, Columbia University. Pp. 344; 153 illustrations. New York: Paul B. Hoeber, Inc., 1936. Price, \$5.50.

THERE is nothing to criticize adversely in this book. It is splendidly bound, printed on heavy enamel stock and in large clear type. The 153 illustrations are without exception models of art, clarity and critical selection. Needless to say, the entire field is covered. The literary style is crisp and the thoughts are therefore easily followed. The subject matter is down to date. The sections on treatment will appeal particularly to the practitioner; they are ample and yet not verbose. In short this book will remain for years as a model for bringing the dermatology of children to the pediatricist, concisely, adequately and pleasantly. F. W.

INTERNATIONAL CLINICS. Vol. IV. Forty-sixth Series, 1936. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, Md., with 14 Collaborators. Pp. 351; many illustrations and one colored plate. Philadelphia: J. B. Lippincott Company, 1936.

Most striking in this issue are the colored illustrations of gastric lesions as seen by the gastroscope. Even with allowance for considerable diagrammatization, the potentialities of this method are shown obviously to be far from exhausted. "Xerostomia" in the Table of Contents proved disappointing when the text was found to add but little to the subject, xerostomia. Except for two progress articles on dermatology, the topics are all medical. E. K.

COSMETIC DERMATOLOGY. With dictionary of ingredients; discussion of anatomic physiologic, and pharmacologic bases of cosmetic application; "shelf-tested" formulary; and appendices on odor and color in cosmetics. By HERMAN GOODMAN, B.S., M.D. Pp. 591. New York: McGraw-Hill Book Co., Inc., 1936. (No price given.)

It is clear that this book was designed primarily for the "dermatologist" of the beauty parlor. The dermatologic physician is only incidental; for example, there are sections on "head and body lice," "clothes lice" and "pubic lice." In many places the literary style drops to that of colloquialism such as "sales of clay go drooping with stock market averages." Nevertheless this is a unique work in a department of dermatology which is a definite part of medical dermatologic practice. Methods in cosmetology are not uniform among American dermatologists, and nothing has been seriously undertaken thus far to collect the data, analyze and record them. Doctor Goodman has done this. He has now supplied a place where dermatologists may check their position and a given point of departure for future condensation and supplementation of data of this sort.

About one-third of the book is really a pharmacopeia adapted to needs in cosmetology. Thereafter, the treatment of specific conditions is taken up as indicated by the following headings:—acne and facial blemishes, baldness, bleaching, cleansing creams and lotions, depilatories, face powders and rouge, hair dyeing, lip and nail preparations, shaving accessories and sunburn. Any author is on treacherous ground when writing in a border line field between legitimate medicine and such lay fields as cosmetology, physical therapy, and so on—particularly at the present day when so many non-medical "experts" are conducting a guerrilla invasion beyond their own province. Acne vulgaris and "facial blemishes" (melanotic moles!) are in point, involving as they do problems in differential diagnosis which may concern important general constitutional states like tuberculosis and cancer. It is trusted that this serious danger will be taken care of in Dr. Goodman's book. In any event, the volume is a miniature encyclopedia which stands alone in its field and to which the dermatologist will be constrained to turn frequently.

F. W.

NEW BOOKS.

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PROGRESS OF MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF
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TUBAL DISEASES AND PELVIC INFLAMMATIONS.

OF all the diseases which may affect the Fallopian tubes, inflammations are the most common and in this group the gonococcus is the most frequent causative agent. It is too often assumed, however, that the gonococcus is exclusively responsible for tubal and pelvic infections; other organisms are frequently of great etiologic importance affecting not only the diagnostic signs but also the choice of treatment. This subject has been well presented by Aldridge¹ based on his experience at the Woman's Hospital in New York. He states that 70 to 75% of all cases of salpingitis are gonorrheal in origin, but by the time the patients come under observation, the cause cannot be determined in a high percentage of cases. The disease is a self limited one which tends to heal spontaneously by autosterilization and in about 85% of cases healing would be complete provided reinfection could be prevented. Infections other than specific ones, are caused by organisms which may continue to live in the tissues for indefinite periods of time, regardless of symptoms but they also tend to heal spontaneously. Nature's success in healing such inflammations depends upon the type of infection and the period of time allowed for healing to take place. Death from general peritonitis caused by extension of infection from the tubes or their rupture is extremely rare. Accepting the foregoing facts, it is obvious that any attack of such inflammation should first be treated by palliative means and most gynecologists are becoming more conservative as time goes on. The result has been a great increase in the number of spontaneous cures, proving that many operations previously done were unnecessary. In Aldridge's experience protein therapy has proved very efficacious and has often kept patients sufficiently symptom-free to enable them to continue with their routine duties while healing was going on. In general, palliative hospital treatment consisted of rest in

bed until the patients were afebrile and subjective symptoms had practically disappeared. During this time the inflammatory exudate usually became absorbed. About half of the attacks were treated by protein injections using sterilized cow's milk. Sedatives and hot or cold applications to the abdomen were used as necessary to relieve pain. Warm vaginal douches were given routinely, not only relieving pain but assisting in the absorption of the exudate. An effort should be made to eliminate infections of the external genitalia from which recurrent infections might occur. If collections of pus bulge in the vaginal vault, they should be opened by posterior colpotomy. Operation may be required in the chronic stage of the disease for recurrent attacks of pain and disability but not merely because palpable adnexal masses are present. In his series of 1021 attacks treated by palliative methods, approximately one-half (48%) either healed completely or became free from symptoms so that operation was not necessary; $\frac{1}{3}$ persisted after treatment with symptoms and palpable masses some of which had to be operated upon. The practice of operating to cure salpingitis in the acute stage is absolutely condemned. Nearly $\frac{1}{2}$ of such operations are unnecessary, if cases are first treated by palliative means. Furthermore, patients operated upon in the acute stage are subjected to unjustifiable morbidity and mortality, unnecessarily destructive surgery and to too high a percentage of unsatisfactory end results.

Heat Treatment. For many years the use of heat has been one of the most important palliative methods for the treatment of pelvic inflammations, but until comparatively recently it was used chiefly in the form of hot douches. With the advent of various types of electrical apparatus, as was to be expected, new methods of applying heat to the pelvic organs have been evolved. One of the most popular is the Elliott treatment, which supplies a hot water bag to the vagina under controlled conditions. Through the rubber bag, inserted into the vagina around the cervix, is circulated a current of hot water maintained at a constant temperature which is never allowed to go above 130° F. The average time for a treatment is 1 hour but this may be varied in accordance with the tolerance of the patient. This treatment causes a marked hyperemia in the pelvic tissues, an average increase of 17% in the leukocytes and an elevation in the temperature of the vagina, uterus, rectum, bladder and pelvic peritoneal cavity of from 5 to 7° and a profuse discharge from the cervix and vagina. Counseller,⁶ trying this method at the Mayo Clinic, states that a high percentage of chronic infections of the pelvis can be clinically cured by it but that there is a fairly constant small percentage of cases in which operation will be required.

Randall¹⁷ comments that there are cases of pelvic inflammation in which the vaginal bag does not radiate heat sufficiently to the affected viscera, either because of the inability of the patient to stand sufficient distention of the bag or by reason of the extent and situation of the infection. This is particularly true of parametritis with perirectal involvement and of high-lying tuboövarian infections. These pelvic conditions have recently been treated by means of a bag designed to apply heat through the rectum in addition to the usual vaginal application and from his experience this method of treatment seems to be of distinct advantage in hastening resolution. The applicator is constructed to permit sufficient distention to fill the lumen of the rectum,

so that heat can be applied to the structures lying anterior to the rectum. The bag is well lubricated and inserted into the rectum and pushed above the dentate margin before it is distended, otherwise the rectum will tend to expel the bag. The bag is distended with water at a pressure of between 2 and 3 pounds and the temperature is kept between 120 and 125° F. for 1 hour. It will cause some redness and edema of the rectal mucosa but no ulceration or necrosis. (All trauma should be avoided. Any form of bag which distends the vagina or rectum should be used with caution. Inflamed adnexa frequently become adherent posteriorly or in the cul-de-sac and forcible dilatation of either the vagina or rectum may result in liberation of pus and be followed by an exacerbation. C.C.N.)

The divergent opinions as to the therapeutic value of diathermy in the treatment of pelvic inflammatory disease may be due to variations in the technique of its application. Horowitz, Derow and Bierman¹⁴ state that there is no method by means of which one may determine the degree of tissue heating which occurs during a diathermy treatment of the pelvis other than by direct thermal measurement. The reading of the milliammeter is no direct guide, because the heat produced by the passage of the high-frequency current varies with the extent of the area of tissue in contact with the electrode, the shape of the electrode, the character of the tissues traversed by the current, the integrity of the local circulation, the effectiveness of the thermoregulatory mechanism of the patient as well as the duration of the current flow. The only way to know the temperatures obtained during a treatment is by actual measurement. These have been made by means of a vaginal electrode equipped with a thermometer. In 255 treatments, the average maximal temperature was 108.8° F. attained 19 minutes after the beginning of the treatment. At the end of treatment, usually after about 45 minutes, the vaginal temperature averaged 107.5° F., while the highest temperature recorded during any treatment was 112.5° F. By means of mercury thermometers in the cervix, bladder and rectum, the temperatures developed in these parts were found to follow closely the vaginal temperature, averaging but 1 or 1½° lower. They believe, therefore, that the reading of the thermometer in the vaginal electrode is a true indication of the temperatures attained in adjacent tissues and also that "trans-pelvic diathermy" by external plate electrodes is effective as a method of pelvic heating.

In addition to the local application of heat by various means, there has been some work done of late in developing heat by means of fever therapy. In reporting their observations along this line, Desjardins, Stuhler and Popp⁷ state that many observers have noted an inhibitory effect of high temperature on gonococcic infections. Experimental work of others which showed that a temperature of about 107° F. killed 99% of gonococci in 2 hours stimulated them to test the method in cases of gonorrhea, both acute and chronic, with or without complicating lesions. Of 29 patients treated, 25 were cured with complete cessation of urethral discharge, disappearance of symptoms and of gonococci in spite of repeated examinations. They are convinced that a large majority of female patients who have gonococcic infections can be cured by this method in much less time than by the methods previously used. Of course it should be remembered that a temperature of from

106 to 107° F. maintained for from 5 to 8 hours taxes the strength of the average individual to a considerable degree. If measures to prevent it were not taken, considerable loss of weight and strength would occur and would probably continue for several days. The loss of weight would result from the loss of fluids by perspiration, and the loss of strength would result chiefly from the loss of chlorides. This difficulty is obviated by causing the patients to drink, during each session of treatment, from 2 to 5 liters of a 0.6% solution of sodium chloride. As a result of this procedure, the weight of the average patient actually increases during a treatment session, and the incidental fatigue usually disappears within 24 hours. Their scheme of treatment is to raise the patient's rectal temperature to 106° F. and to maintain it between that and 107° F. for 6 hours at each of the two initial sessions of treatment, which are regarded as test sessions. If by this time the urethral discharge has ceased and gonococci have disappeared from smears, one or two additional sessions of fever are given in order to prevent any possibility of recurrence. If the discharge has not ceased after the second session, the subsequent sessions are extended to 7 or 8 hours, it seldom requiring more than four sessions to effect a cure. All of these treatments are carried out by means of the air-conditioned fever chamber known as the "Kettering hypertherm." Treatment of this kind requires the constant attention of nurse technicians, who must be carefully selected and specially trained. There must also be the constant supervision of a physician familiar with all the details of the method. The nurse must not leave the patient for an instant while the patient is in the chamber unless she is relieved by another nurse or physician.

A combination of systemic and local heating has been used with very satisfactory results by Bierman and Horowitz.² The technique they employ consists in the use of pelvic diathermy while the patient lies within a hood containing carbon filament lamps. By means of diathermy alone it is possible to maintain a temperature in the vagina of 108° F., which is 8° above the normal. The temperature of the cervix, as indicated by a thermocouple needle inserted into it, becomes elevated to within about 1.5° of the temperature registered by the vaginal electrode thermometer. The additional use of a cabinet surrounding the body, containing photothermal lamps, causes a rapid elevation of general body temperature, because of the prevention of heat loss from the body and the introduction of further heat energy into it. This combined use of heat by diathermy and phototherapy is usually sufficient to cause an elevation of the mouth temperature to from 105 to 106° F., within 1½ hours. The vaginal temperature is then easily raised to 111 or 112° F., and these temperatures are maintained for from 3 to 4 hours. The sensations of the patient undergoing treatment are those usually experienced during hyperpyrexia induced by high-frequency currents. There is sometimes a sensation of pelvic warmth, but the patient is usually conscious only of a diffuse heating of the entire body. During the period of transition from normal temperature to 104° F. there is usually restlessness and general discomfort for which morphine or a barbiturate may be given but there is no pain at any time. They have wisely accepted for treatment only patients in good general condition, without cardiovascular or pulmonary disease or marked obesity. Treatments are not administered 4 days before the

expected menstruation, during the period, or for 3 days afterward. Pregnant patients have not been treated.

Other Non-operative Treatments. For several years certain investigators in Germany have been injecting living gonococci into patients suffering from gonorrhea. From a 4-year experience with this treatment, comprising over 300 injections, Schultz¹⁹ states that there is no danger of a general septicemia from such a procedure, and he believes that, while this form of treatment is not successful in every case it is a valuable addition to the therapy of gonorrhea. He warns that the treatment is contraindicated in the presence of a high temperature such as frequently accompanies acute pelvic inflammatory disease but the slight fever of subacute and chronic pelvic inflammatory disease may be disregarded. In his series 95% of the patients were in the chronic stage and of these 74% were discharged as cured after from 1 to 4 injections at 10-day intervals.

Believing that estrogenic substances stimulate the defensive mechanism of the pelvic organs, Fluhmann and Hoffmann¹⁰ injected amniotin in a series of 29 adults with acute or chronic pelvic inflammatory disease. In 23 instances there were definite palpable adnexal masses at the time the treatment was begun. After the treatment, from 2 to 6 weeks later, complete healing with disappearance of the masses was noted in 7 cases while 9 others were improved but still had palpable masses. In 7 cases there was no improvement, of which 5 were subsequently operated upon. Of 6 patients who had no masses before treatment, only 3 showed any improvement from the treatment. While these results are interesting, the series is too small to be of much value, and besides many of these pelvic masses subside even if no treatment of any kind is given except rest.

The intramuscular injection of sterile milk is often of value as was stated in the beginning of this review. Greene¹¹ extols the value of this treatment and states that the injection of milk is followed by a leukocytosis, usually within 4 hours. He has found that the patients feel better, gain in weight and continue their routine work after the injections and major operations are sometimes avoided. Pre-operative injections of milk make operation somewhat less difficult and abbreviate the period of convalescence. In 18,270 injections given over a 5-year period there has been no evidence of untoward effect in any individual. In his work he used skimmed milk boiled for 20 minutes and allowed to cool. The first dose was 5 cc. injected intramuscularly and each subsequent dose is 10-cc. repeated at weekly intervals.

Since the most important principle in the non-operative treatment of pelvic inflammatory disease is the induction of pelvic hyperemia, Jacoby¹⁵ proposes the use of one of the drugs recently made available which produce vasodilatation and thus induce hyperemia. He suggests the use of acetyl-beta-methylcholine-chloride which, when taken by mouth in doses of 100 to 200 mg., produces generalized flushing and sweating, increased salivation, a lowering of blood pressure, increase in pulse rate, intestinal peristalsis and metabolism, which last from $\frac{1}{2}$ to 1 hour. Subcutaneously in doses of from 5 to 25 mg. the same effects are greatly increased except that the action on the gastrointestinal tract is less pronounced. When applied locally by iontophoresis, there is some general reaction but a much more pronounced

effect at the site of application. Of 10 patients treated in this manner, 7 were completely cured although they had extensive pelvic inflammation. He believes that this method is an effective agent in promoting the rapid absorption of inflammatory pelvic exudates with relief of symptoms and seems superior to other methods of exciting pelvic hyperemia because it has a much more sustained physiologic action. (Rest, preferably in the modified Fowler position, proper diet, avoidance of all trauma, and the non-traumatic application of heat are the sheet anchors of treatment of acute pelvic inflammatory disease and under this treatment the majority will subside. Too energetic treatment is unwise. C C.N.)

Operative Treatment. It is often important, but at the same time sometimes difficult to differentiate between an acute salpingitis and an acute appendicitis. In a study of 19 cases of acute salpingitis and 38 of acute appendicitis, Smith, Harper and Watson²⁰ found that the sedimentation time of the blood may be of value in differentiating these two conditions, if the duration of symptoms when the test is made is taken into consideration. During the first 24 or even 48 hours after the onset of symptoms, the sedimentation time is apt to be shorter in acute salpingitis than in acute appendicitis; an occurrence that is not unfailing, but frequent enough to be given consideration, as it is more uniform than either the leukocyte count or the differential. They believe that this may be due to the difference in the two organs as regards their function and nerve supply. The appendix is supplied by both sympathetic and parasympathetic fibers. Gastro-intestinal symptoms occur for some time before there is any tenderness localized over the region of the appendix. Furthermore, the appendix is a vestigial organ capable of only slight distention before it causes symptoms. The Fallopian tube has only sympathetic nerve fibers and is a functioning organ which is capable of relatively great distensibility before causing symptoms. They show that with the duration of the infection the sedimentation time becomes shortened in the case of acute appendicitis and that is probably what happens also in acute salpingitis. But in the case of salpingitis the infection progresses further before giving symptoms. Therefore, the sedimentation time in acute salpingitis is shorter in the first 24 to 48 hours *after the onset of symptoms*, because the infection has been there many hours before it began to cause symptoms.

If acute appendicitis is present, of course immediate operation should be done, but if acute salpingitis is present, most gynecologists advise conservative non-operative treatment during the acute stage, as most of such cases subside. However, the occasion will arise when an abdomen is opened for acute appendicitis and acute salpingitis is found instead. What should be the proper procedure to follow under such circumstances? Conservatives advocate closure of the abdomen without disturbing the tubes; radicals advise extirpation of the tubes. The plan advocated by Elgart⁸ is to ligate the abdominal ends of the tubes to prevent further contamination of the pelvic peritoneum. Following such operation the clinical signs rapidly improve; and, since the uterine ends of the tubes are open, there is good drainage at that point into the uterus and therefore no pyosalpinx will result. He has had occasion to see the results of such a procedure at secondary operations and found that the tubes remain slightly thickened. Of course such an operation

sterilizes the patient, but salpingitis frequently does also. If desired, a salpingostomy may be done at a later date to reestablish the abdominal opening of the tube.

Halter¹² of Vienna states that the indications for operation in chronic pelvic inflammatory disease are: first that the patient shall have had at least 6 months conservative treatment without results, and second the expressed wish of the patient to be relieved by operation because of her painful symptoms. Operation is never performed until it is fairly certain that no latent infection exists, which means that the patient's temperature shall have been normal for at least 6 weeks and that the blood sedimentation test shows a rate over 1 hour. Of the patients admitted to this clinic only 9.2% were operated upon. Halter's study has shown that when operation is done better results will be obtained from the radical than from the conservative procedure. Thus the mortality of the radical operation was 1.7% as against 2.6% for the conservative procedure. With total removal of the pelvic organs 98.4% of the patients remain free from symptoms whereas only 42.1% of the patients who have had conservative operations are completely relieved. He believes that no patient should have a conservative operation who has cystic degeneration of both ovaries and he advises removal of a healthy tube if the opposite one is diseased, in order to forestall the later development of pain in the conserved organ, since the probability of pregnancy in these patients is slight, being only 10% in this series. In brief, his advice is "don't operate until you must and the patient is in good general condition, but when operation is done, make it radical." (There is no question as to the soundness of this advice as far as elderly women are concerned. In young women, bilateral salpingectomy and conservation of the ovaries and uterus, in properly selected cases, has given good results. Obviously cases should be carefully studied and individualized. No hard and fast rule will be suitable for all. C.C.N.)

Since tubal infections tend to sterilize themselves if reinfection can be prevented, Falk⁹ proposes an operation which prevents reinfection and also conserves the tubes. The operation consists of resection of the cornual ends of both tubes thus interrupting the pathway of infection from the uterus to the tubes. In leaving the infected tube in the abdomen no fear is felt because since it cannot be reinfected it will undergo resolution. This operation has the advantage over salpingectomy in that there is less risk of interference with the ovarian circulation. In 75 cases in which the operation was performed, 67% were cured, 24% had slight residual symptoms and 7% had definite complaints after the operation.

Those familiar with pelvic inflammatory disease will recognize that a problem often arises in the management of those patients in whom subsidence of fever does not occur after proper treatment. In most cases sustained fever indicates active suppuration, and since laparotomy for the removal of affected structures carries an excessive mortality in cases of this type, it often becomes necessary to institute drainage. When drainage becomes necessary, Cooke⁵ lists four possible means of approach, three of which are more or less orthodox. First may be mentioned the usual posterior colpotomy which has a very low mortality. Second, anterior colpotomy may be done in the occasional case in which the collection of pus lies anterior to the uterus or broad

ligament. Third, ordinary open laparotomy through uncontaminated peritoneal cavity may be done but this gives an almost prohibitive mortality. The last method which he mentions and has employed to advantage consists of approach by small incisions through the abdominal wall to areas of suppuration which are inaccessible by either of the vaginal routes. An effort is made to locate the incision over a point at which the parietal peritoneum is adherent to the underlying structures in order that the previously uncontaminated peritoneum may not be traversed. If the incision should enter the free peritoneal cavity, the site of adhesion of the inflammatory mass to the parietal peritoneum is located by digital exploration, the first incision is closed and a new incision is made over a safe point in the adherent area. If no point of adhesion is found, the parietal peritoneum is sutured to the diseased structures and the wound is packed with gauze; on the next day, the gauze is removed and the abscess is opened through the walled off sinus formed by this procedure. If desired, the diseased structures may be removed several weeks after drainage; but his experience has shown him that this secondary operation is often extremely difficult and that the patients who do not have the secondary operation often do better than those that are reoperated upon. Therefore he has practically abandoned secondary operation and advises against it.

Streptococcus Infection. It is now rather generally understood that while the gonococcus usually is the cause of salpingitis and tuboövarian abscesses, the streptococcus does not involve the lumen of the tubes but causes a pelvic lymphangitis or cellulitis and this is an extra-peritoneal lesion. This disease process can terminate in one of three ways: if the virulence is very great the patient may soon die by the overwhelming toxemia; in many cases, the patient has sufficient resistance to overcome the infection and complete resolution occurs; in the third group, after a more or less stormy battle, the cellulitis undergoes abscess formation which requires surgical incision for its relief. Such an abscess may be opened by posterior colpotomy being careful not to invade the peritoneal cavity; but as Brady³ points out in a lucid description of this subject, such an operation is beset with several dangers. If the forceps which is used to penetrate the broad ligament should perforate it there is immediately the danger of a streptococcic peritonitis. Moreover, in tunnelling the instrument laterally from the colpotomy incision toward the broad ligament there is danger of injury to the ureter or uterine artery. A second method of drainage is the inguinal route. This consists of making what amounts to a McBurney incision until the peritoneum is reached. The peritoneum is not opened but is pushed toward the median line and an extraperitoneal finger dissection is made until the diseased area in the broad ligament is reached. Brady prefers this latter method of drainage since these patients left the hospital on the average of 29 days after operation as against those drained by the vaginal route who remained in the hospital an average of 47 days after operation. Several of the patients in this series later became pregnant showing that this type of infection does not cause sterility but it is not safe for them to become pregnant too soon after such drainage because the streptococcus remains dormant in their tissues for quite some time and may cause a recurrence of the

cellulitis as a result of the congestion and stretching of the broad ligament which accompanies a pregnancy.

Other Types of Infection. Stein²¹ calls attention to a safe and simple method of diagnosis and treatment of *tuberculous salpingitis*. Whenever this condition is suspected, he believes that it is advisable to use oxygen pneumoperitoneum for diagnostic roentgenography since oxygen will serve the additional purpose of being a valuable therapeutic agent. The patient usually shows prompt evidence of improvement, the temperature falls to normal within a few days, the pain is less, the patient feels stronger and begins to gain weight at once. In some instances a single insufflation suffices, in others repeated treatments are used in periods of from 4 days to 2 weeks. He recommends weekly insufflations of about 1 liter each, the number depending upon the results obtained. The patients are kept in bed from 18 to 24 hours after every injection for diagnostic purposes. In cases injected for therapeutic purposes they are usually bed patients in the beginning of treatment. When the temperature reaches normal they are kept in bed for 48 hours after each treatment. The rationale of this treatment is based upon the good results which have been obtained by exploratory laparotomy and exposure of the tissues to air. Pneumoperitoneum by the injection method spares the patient the danger and pain of a laparotomy. If no beneficial effects are noted after a fair trial, operation may still be done, the gas having done no harm. (The judicious use of the Roentgen-ray as recommended by the late Dr. J. O. Polak is worthy of a trial in cases of tuberculous salpingitis. C.C.N.)

Pneumococcus infection of the pelvic organs in women is discussed by Tompkins,²² who reports 3 cases of this type. He states that the respiratory tract is the probable source of the pneumococci, but the route by which these organisms reach the peritoneal cavity is often a matter of conjecture. The two most likely possibilities are metastatic infection by either blood or lymph stream or ascending infection through the genital tract. The disease usually begins with a slight chill, sudden severe cramping lower abdominal pain, diarrhea and vomiting. High fever, high leukocytosis (30,000) with high neutrophil count (95%) and rapid pulse soon follow. Abdominal rigidity is often not marked. Abdominal distention and constipation often appear and are frequently accompanied by bulging in the cul-de-sac, because pneumococci rapidly produce large quantities of pus. Material for bacteriologic examination may be obtained by vaginal or abdominal puncture. The typical pus is profuse, thick and odorless and contains the organisms in pure culture. The prognosis of localized infections or abscesses that can be drained or removed *en masse* is good; but in other intraabdominal pneumococcus infection the outlook is grave. The present trend of treatment of the generalized pneumococcus peritonitis is away from laparotomy in the hope that localization will occur. Specific remedies which have been suggested such as optochin, bile salts, autogenous vaccines and antipneumococcus serum have not been employed in a sufficient number of cases to permit evaluation.

King¹⁶ reports that he has had 3 cases of this type and presents 11 additional ones which he has collected from the literature. There are two points which he emphasizes in the diagnosis. In many cases there

is often a previous indisposition usually associated with the symptoms of an upper respiratory infection and careful inquiry on this point should always be made. Another distinguishing point is the rapid formation of pus which takes place earlier and in far greater quantity than in peritonitis from other causes. Of course, pneumococcus peritonitis in children is by no means a rare condition but the condition which we are now considering in adult women has seldom been encountered.

A case of *blastomycosis* of the Fallopian tube and uterus has been reported by Hamblen, Baker and Martin¹³ in a patient with arrested pulmonary blastomycosis. They were unable to find any similar case previously reported in the literature. The diagnosis was made from curettings and culture. The tissue reaction was much like that in tuberculosis except for the presence of the double-contoured blastomycetes. The treatment in this case consisted of radical removal of the diseased structures which was followed by an uncomplicated post-operative course.

Cancer of the Tubes. In reporting 2 cases of primary cancer of the tubes, Charache⁴ reveals that he searched the literature and found that 323 such cases had been reported. It occurs in about 0.45% of all genital tumors and chronic inflammation is supposed to be a predisposing factor. Diagnosis is extremely difficult and is often missed even at operation unless the tumor is sectioned by the surgeon. As aids in diagnosis there are the presence of serosanguineous discharge with various menstrual disturbances, abdominal pain associated with a palpable adnexal tumor and a negative uterine curettage. The treatment of choice consists of radical surgery with removal of both tubes and ovaries and a complete hysterectomy with wide excision of the broad ligaments. This should be followed by Roentgen ray therapy. The prognosis is very poor, since only 7 cases in this collected series survived longer than 3 years.

Three cases of primary cancer of the Fallopian tubes are reported by Robinson¹⁸ who states that this condition is frequently bilateral and therefore the apparently normal looking opposite tube should not deter us from removing the organs in a radical manner. The outer two-thirds of the tubes are the sites of greatest predilection. The fimbriated ends become closed late in the disease in contrast to what happens in salpingitis and then the tube may reach enormous proportions due to distention with secretions and necrotic tissue elements. The most common complaints are pain in the lower abdomen and yellow, watery or bloody vaginal discharges. The character of the pains is apt to be intermittent and they may disappear after a sudden gush of fluid from the vagina, in this respect resembling a *hydrops tubæ profluens*, which of course, is of inflammatory origin.

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PHYSIOLOGY

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SESSION OF FEBRUARY 15, 1937

Studies of Heart Muscle in Tissue Cultures. M. J. HOGUE (Laboratory of Anatomy, University of Pennsylvania). Heart muscle from 8-day chick embryos was grown in tissue culture for 180 days. The medium was a combination of Locke and Tyrode solutions, chicken bouillon, and embryonic extract. In it 94.5% of the explants grew; 65.4% of these showed growth of muscle cells; 65% of the muscle-cell cultures contained cross striated myofibrillæ when fixed and stained. Myofibrillæ with striations were seen in living cultures and in the same preparations after they were fixed and stained. Most of the cardiac muscle cells were unicellular, a few were binuclear and a very few multinuclear.

The cardiac muscle cells showed great individual variations in their rate of contraction. The rate varied from 2 to 244 contractions per minute, depending largely on the temperature and the age of the culture, though other factors were involved. As the cultures cooled below 33° C. the beat became slower and finally stopped. The rate of contraction was most rapid in cultures from 15 to 60 days old. In older cultures the rate became slower. The oldest culture to beat was 158 days old.

Factors Concerned with the Toxic Action of Chloroform on the Liver. H. M. VARS, S. GOLDSCHMIDT, and I. S. RAYDIN (Laboratory of Physiology and Harrison Department of Surgical Research, University of Pennsylvania). It has long been known that certain of the volatile anesthetics, notably chloroform, could produce damage of the liver following inhalation. Opie and Alford (1915) showed that a high-carbohydrate diet previous to the anesthesia afforded a degree of protection to the liver of rats which received chloroform. While a carbohydrate diet reduced the incidence of liver necrosis, a fat diet was found to increase the susceptibility of the liver to the damaging effects of this anesthetic. This observation was confirmed upon dogs by Davis and Whipple (1919). These findings have received further confirmation in our hands with both dogs and rats.

The protective action of a high-carbohydrate diet has generally been ascribed to the increase of liver glycogen which results from the diet. Our studies show that the principal cause of the protective action exerted by the increased liver glycogen is not the presence of the glycogen *per se*, but results from the reduction of liver lipid as a result of glycogen deposition on a high-carbohydrate diet. Within certain limits, the Rosenfeld hypothesis holds, namely an increase in liver glycogen is accompanied by a reduction in hepatic lipid. However, this rule is not invariable for we have been able by appropriate feeding to obtain animals in which the liver showed both a high-glycogen and a high-lipid content. As a result of these experiments we have concluded that, over a wide range, regardless of the liver glycogen content, if the fatty acids exceed a value in rats of between 15 and 20%, liver damage will usually result from the administration of chloroform.

The amount of liver lipid, therefore, conditions the amount of the fat-soluble chloroform which is taken up by the liver, and therefore determines the amount of the toxic agent present and the duration of the toxic action.

Identification of Blood by Hemolytic Methods. M. H. JACOBS, H. N. GLASSMAN, and A. K. PARPART (Laboratories of Physiology, University of Pennsylvania, and of Biology, Princeton University). Differences in the behavior of the erythrocytes of different species in solutions of certain penetrating substances are so great and so constant that frequently a given sample of blood may be identified by methods depending on osmotic hemolysis alone. The larger groups of vertebrates show characteristic differences in the relative rates of hemolysis in water and in appropriate solutions of ethylene glycol, glycerol and urea, respectively. Within a single class, such as the mammals, a further separation of species is possible by means of solutions of mannitol, erythritol, xylose, NH_4 tartrate, NH_4 borate and NH_4Cl , with and without NH_4 benzoate. By the use of these and certain additional characters such as the effects on permeability of NaHCO_3 , CO_2 , and traces of Cu, the direct hemolytic effects of bicarbonates, and differences in osmotic resistance in solutions of NaCl and KCl, it has been found possible to construct an analytical key which permits the identification of all of the 20 species of mammals that have so far been carefully studied. The fact that species are so readily distinguishable by characters of this sort indicates a high degree of specificity in the constitution of the cell surface which has important consequences for theories of cell permeability.

The Effects of 10 Commonly Used Drugs on Basal Cardiac Output, Metabolism, Blood Pressure, Heart Size, Respiration, and the Electrocardiogram in Over 100 Patients. C. J. GAMBLE, I. STARR, A. MARGOLIES, J. S., DONAL, JR., N. JOSEPH, and E. EAGLE (Departments of Research Therapeutics, Pharmacology, Robinette Foundation, and Medical Division of the Hospital, University of Pennsylvania). The action of commonly used drugs on the cardiac output, size, and rate, on the blood pressure, on the metabolic rate, on the respiration, and on the electrocardiogram has been ascertained and described.

The subjects consisted of over 100 patients suffering chiefly from cardiac or circulatory disease but not from congestive heart failure. Estimations were made under conditions of basal metabolism. The results have been subjected to statistical analysis.

The drugs studied included digitalis, epinephrine, ephedrine, caffeine, theophylline, carbaminoylcholine, sodium nitrite, nitroglycerine, pitresin, quinidine, morphine and strychnine.

The action of these drugs is almost altogether similar to expectations based on animal experiments.

Pancreatectomy in the Pig. F. D. W. LUKENS (Cox Institute for Metabolic Research, University of Pennsylvania). Nine young pigs, weighing 5 to 15 kg., were depancreatized. The average survival was 9 days. When fasted, glycosuria was slight or absent, and the nitrogen excretion, although double that of fasted controls, was low. Ingested carbohydrate was quantitatively excreted. Ketonuria was marked but was not associated with acidosis. The injection of crude alkaline pituitary extracts caused death in acidosis and coma with greatly increased serum lipoids.

The results have been compared with pancreatic diabetes in other species and with the findings in Houssay animals. Pancreatic diabetes may differ from the picture seen in the dog (*a*) by the selection of species or (*b*) by the simultaneous removal of other endocrine glands in a single species. The suggestion is offered that the apparently mild diabetes of the pig is due to the nature of its pituitary (or other endocrine) function rather than to the utilization of carbohydrate in the absence of insulin.

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if a normal duodeno-pancreatic graft is placed in the neck there is no fall in the raised blood sugar (Fig. 10); 2, if insulin is injected there is a diminished and more transitory fall in the blood sugar compared to the normal or pancreatectomized animals (Fig. 11); 3, both normal or hypophysectomized animals treated thus resist high doses of insulin which are toxic for the controls; the presence of gonads, thyroids or adrenal medulla not being necessary for the increase of the resistance.^{57a,114} This resistance to insulin is also

TABLE 1.—BLOOD SUGAR AFTER INJECTION OF HYPOPHYSIS AND ADRENAL EXTRACT. Each number corresponds to the average of determinations made upon 15 to 20 toads (*Bufo arenarum*, Hensell). (Houssay and Foglia, 1936.)

	No. of the experiment.		Injection of 2 principal lobes of toad's hypophysis.	Injection of 0.25 cc. Cortin = Upjohn 10 gm. whole adrenal.	Injection of 1 toad's adrenal gland.	Injection of 0.025 gm. of dog's adrenal cortex.
Adrenals and pancreas removed	1 4	0 107 0 105	0 202 0.187	0 117		
Pancreas removed	1 5 6	0 176 0 179 0 190				
Hypophysis and pancreas removed	1 2 4 7	0 096 0 102 0 100 0 108	0 186 0 156 0 190 ..	0 112	0.106 0 108	
Adrenals hypophysis and pancreas removed	1 2 3 8	0.086 0 108 0.082 0.079	0.142 0.161 0.135 0.138*	0 094	0 113 0.094 0.082	0 086
Adrenals removed	1 4	0 043 0.037	0 046			
Hypophysis removed	1 4	0.015 0 044				
Controls	1 4	0 055 0 053	0 056			

* With only one principal lobe.

present even if the blood sugar is normal. Insulin resistance is due mainly to the tissues. Replacing 85% of the blood of a dog with hypophyseal diabetes with blood from a normal dog, the resistance to insulin is not altered. Replacing 85% of the blood of a normal dog with blood from a dog suffering from hypophyseal diabetes, insulin produces the usual drop in the blood sugar, though the return to normal is more rapid (Fig. 12).

The pancreas secretes less insulin than normally in dogs with anterior pituitary diabetes. If the pancreas of such an animal is

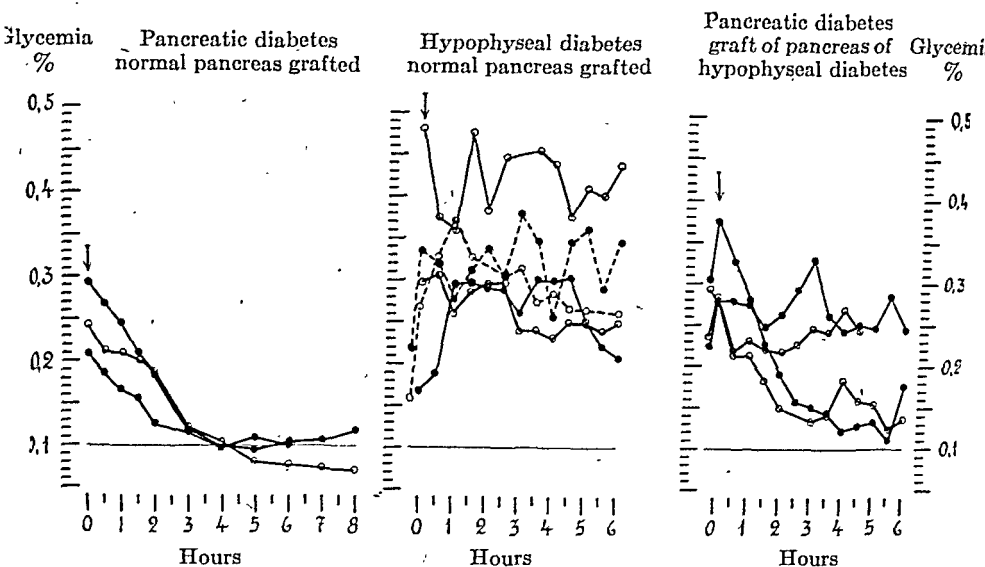


FIG. 10.—Pancreas grafted for from 6 to 7 hours in the neck. (Houssay and Foglia, 1936.)

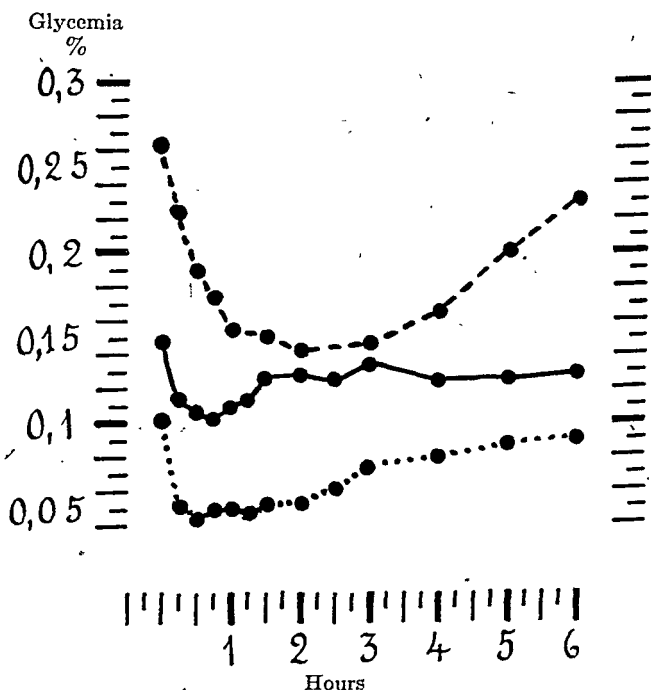


FIG. 11.—Composite curves of glycemia of dogs injected with 2 units of insulin per kg. intravenously.

Thick line 5 dogs with hypophyseal diabetes.

----- 4 dogs with pancreatic diabetes.

..... 5 normal dogs. (Houssay and Foglia, 1936.)

grafted into the neck of a pancreatectomized diabetic dog it causes a slight or fairly considerable fall in blood sugar, but this does not occur with the rapidity as when a normal pancreas is used (Fig. 10).

Certain experiments can be cited as showing that there exists an antagonism or functional balance between pancreas and hypophysis. Krichesky¹²⁵ has found there is an increase in the volume of the islet tissue in the pancreas of hypophysectomized rats. According to Kepinow and Guillaumie^{122a} the pancreatic blood of hypophysectomized animals has a greater blood sugar lowering action than that of the controls. The hypoglycemic action of the systemic venous blood in hypophysectomized animals found by Cowley⁴⁹ has not

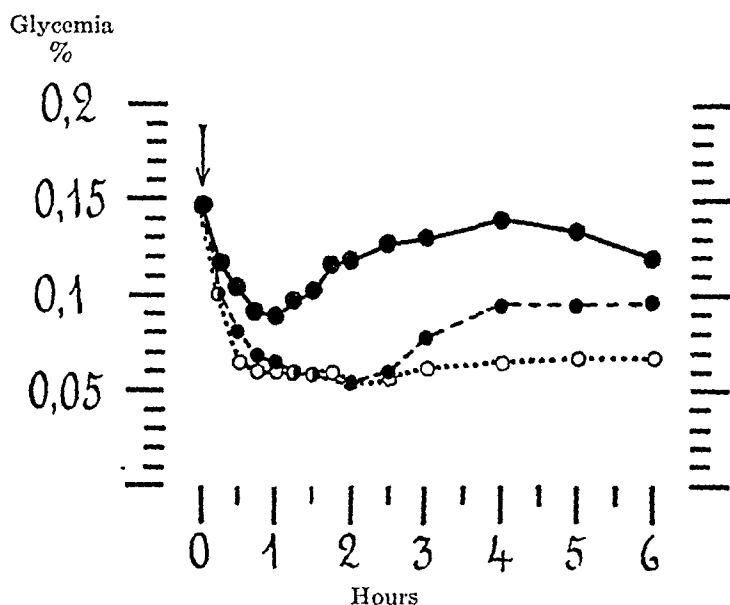


FIG. 12.—Action of 2 units insulin per kg. intravenously on dogs with 3 blood-lettings (3.5% of body weight each), followed by equivalent transfusions.

— 3 dogs with anterohypophyseal diabetes which received normal blood.
 - - - 5 normal dogs which received blood from dogs with hypophyseal diabetes.

..... 4 normal dogs which received blood from normal dogs. (Houssay and Foglia, 1936.)

been confirmed by Di Benedetto.^{57b} The stimulation of the peripheral end of the vagus causes an intense hypoglycemia in hypophysectomized dogs.

Certain facts make one suspect there is hypersecretion of the diabetogenic hormone of the anterior pituitary lobe in diabetes. If blood from a pancreatic diabetic dog is transfused into a normal animal there is a secondary rise in the blood sugar which is not seen if the blood is taken from a pancreatectomized-hypophysectomized animal (Kepinow¹²¹). Transfusion of blood of insulin-resistant subjects who have been treated with insulin does not cause hypoglycemia, but it does so if it is provided by a non-insulin-resistant

subject (Boller, Ueberrak and Falta²⁰). If the blood of diabetic adults is injected into rabbits it renders them insulin-resistant (Wesselow and Griffiths¹⁹⁵). According to Anselmino and Hoffmann^{3a,b,c} the blood of fasting diabetics causes a glycogenolytic action on injection in rats. Normal blood during fasting is inactive but acquires glycogenolytic or ketogenetic actions after a meal rich in carbohydrates. This is not seen in hypophysectomized animals.

In acromegaly, there is frequently a raised blood sugar and glycosuria and there are arguments in favor of its hypophyseal origin.^{107b} Glycosuria and hyperglycemia are frequent in pituitary basophilism but it is not possible to say whether these are due to hyperadrenalism or hyperpituitarism.

Thus in the absence of the pituitary, pancreatic diabetes is diminished, excess of anterior pituitary causes an increase in this diabetes and can even produce an experimental diabetes, and is possibly the cause of acromegalic diabetes. The normal secretion of the anterior pituitary is one of the functional factors which contribute to the complete diabetic picture. Thus one may suppose there is probably some pituitary action in all diabetes. Further experiments should try to demonstrate and measure quantitatively this anterior pituitary factor. The secretion of the anterior pituitary works in antagonistic and reciprocal balance with the pancreas, thus reduction of the pancreatic function favors the anterior pituitary action and *vice versa*.

Adrenal. Neither cortin nor any known adrenal substance has any diabetogenic properties.* Adrenalin causes an immediate hyperglycemia and glycosuria but daily injection for weeks does not bring about diabetes. The adrenal secretion of adrenalin is not necessary for the maintenance of the blood sugar which remains normal in dogs with denervated adrenals or the adrenal medulla removed. A complete summary of the known facts on the influence of the adrenals on carbohydrate metabolism has been published by Leloir in 1934^{131b}.

Adrenalectomy produces hypersensitiveness to insulin^{5, 91, 133, 134, 168, 189} which is also seen if only the medulla is removed^{19a, b, 22, 134} or the gland denervated^{11, 22, 26, 28, 62, 134, 168, 17} in all these cases the hypersecretion of adrenalin, which is stimulated by insulinic hypoglycemia, is suppressed and counteracted.^{28, 116, 131b, 191, 200} The great sensitiveness to insulin of patients suffering from Addison's disease is well known.

The other disturbances in the carbohydrate metabolism produced by adrenal insufficiency are due essentially to lack of the cortical hormone and do not occur immediately but appear in a progressive form. They are: 1, Gradual hypoglycemia which becomes marked only after a certain time;^{131b} 2, rapid decrease and even disappearance of the liver glycogen;^{131b} 3, decrease or retardation of the re-synthesis

* In normal or hypophyso-pancreatectomized dogs or toads.

during rest⁵⁴ of muscular glycogen exhausted by tetanization (Fig. 13), and after injection of glucose⁵⁵ (Fig. 14). 4, Decrease or absence

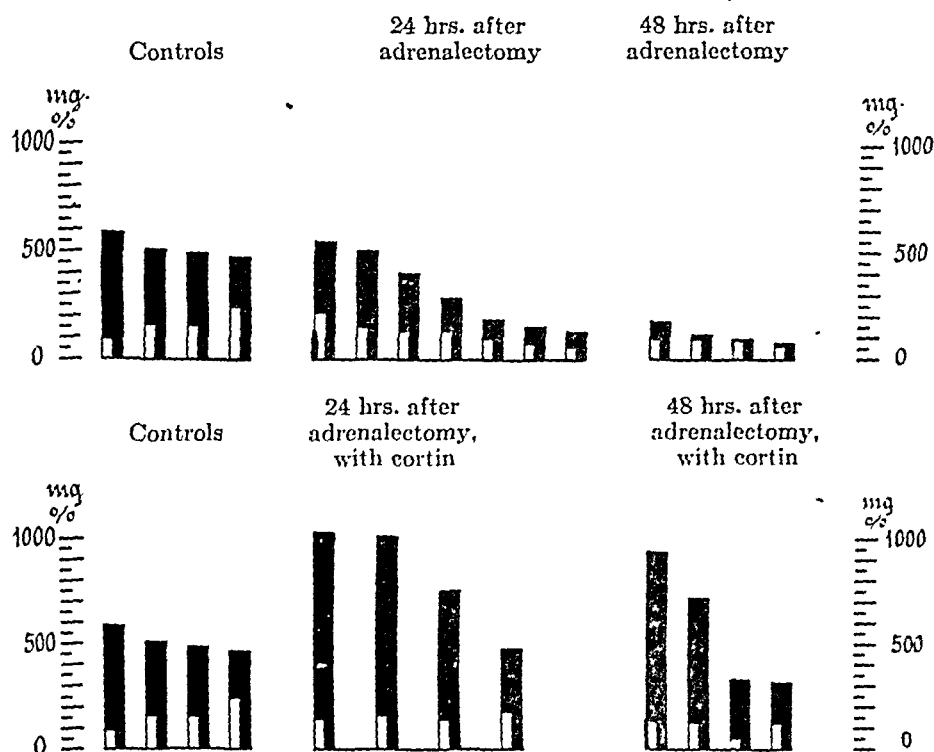


FIG. 13.—Each column represents the average values of muscle glycogen of one dog in mg. per 100 gm. White: immediately after fatigue. Black: after 1 hour rest. (Dambrosi, Leloir, Novelli, 1933.)

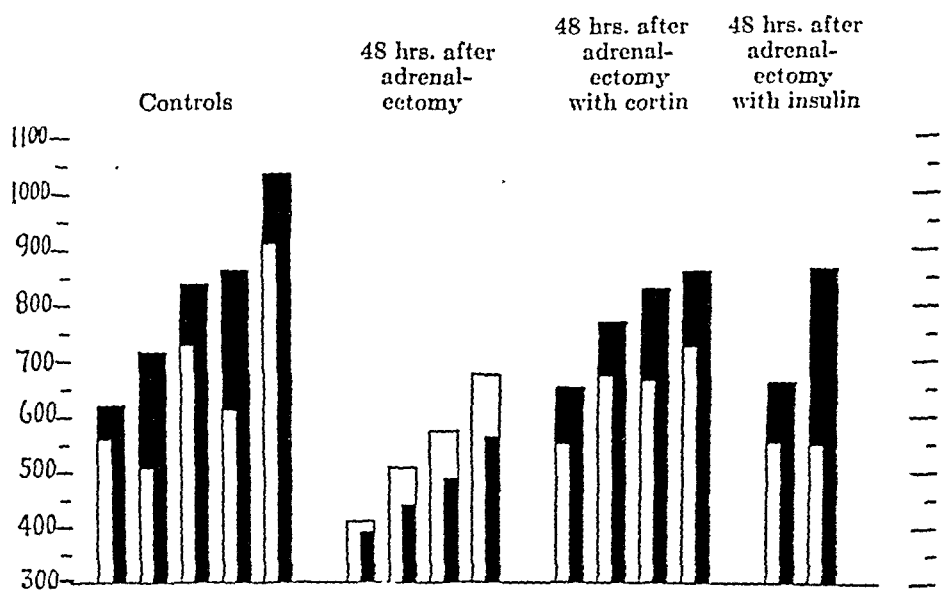


FIG. 14.—Each column is the average muscle glycogen (mg. per 100 gm.) of one chloralosed dog. White: before. Black: after the injection of glucose (2 gm. per kg.) (Foglia, Fernández, Leloir, Novelli, 1933.)

of the ability to form hepatic and muscle glycogen after injection of glucose.⁶⁹ 5, Finally in a more advanced stage, a decrease in the muscle glycogen.

Extract of adrenal cortex corrects all these symptoms and even overcompensates the formation of muscle glycogen^{24,55,69} (Figs. 13 and 14).

The adrenal cortex appears to increase the formation of glucose at the expense of proteins in fasting, in pancreatic diabetes¹³⁹ and in phloridzin diabetes^{67a} and of glycogen during anoxemia.^{67b}

Pancreatic diabetes with all its usual intensity occurs after pancreatectomy in dogs deprived of the adrenal adrenalin secretion, whether this is by previous extirpation of the medullary substance,^{113a} ^{131b,136,192} adrenal denervation, or total removal of the two sympathetic chains.^{135b} The attenuations which have been described after the partial denervation or other operations are usually transitory,^{13,19a,29,70,180,182} and probably due to some unknown traumatic origin. In this way Rogoff and Ferrill (1936) correct their 5 previous papers which describe them. In other cases, the removal of the pancreas may not have been complete.^{33,39,167,194} In human diabetes, certain improvements have been noted,^{38,59,81,184,190} but it is difficult to draw any definite conclusion. Recently Rogoff and Ferrill (1936) have asserted that the secretion of adrenalin diminishes and may even cease altogether during the course of diabetes, thus it is illogical to try and bring this about by operation or radiotherapy.

The influence which total extirpation of the adrenal may have on the development of pancreatic diabetes has been studied. In acute experiments where the pancreas and adrenal are simultaneously removed, the animals remain in bad condition, survive only a short time and have no diabetic hyperglycemia^{2a,74,78,93d,94,147,159,192,194} with rare exceptions,¹³² although this may continue if it already existed.^{93d} Lewis and Turcatti^{135a} have shown, and Leloir has confirmed,^{131a,b} that if one adrenal and then the pancreas is removed and the animal kept in good condition with insulin during healing, on extirpation of the second adrenal and suspension of insulin there is a high diabetic hyperglycemia^{7a,b,84,131,135a} which can be greater than usual^{131a,b,135a} and which persists until death, or slightly diminishes towards the end. Thus the presence of the adrenal is not the cause of the diabetic hyperglycemia in pancreatectomized animals.

Recent experiments show that suppression of the adrenals produces an attenuation of pancreatic diabetes in cats,^{92,139,141} dogs¹⁴¹ and toads.^{103b} Cats have been kept alive by Long and Lukens for 16 days, and in 1 case 28 days, without both glands and with cortin, compared with 4 days in the pancreatectomized animals. There was a marked decrease in the hyperglycemia and glycosuria, scanty ketonuria and no acidosis, no increase in the excretion of

nitrogen and a low D/N ration. Houssay and Biasotti (1936) have observed low hyperglycemia in the pancreatectomized adrenalectomized toad (Fig. 15). The attenuation in the pancreatic diabetes brought about by adrenalectomy is similar to that brought about by hypophysectomy. Three theories to explain these facts can be set forth: 1, the adrenal acts through the pituitary; 2, the pituitary acts through the adrenal; 3, both have independent actions with similar results. Long is inclined to accept the second hypothesis.* In reality cortin or adrenal extract has no diabetogenic action in cats or toads. The administration of the *pars glandularis* of the pituitary did not produce any effect in the cats of Long and Lukens,† but it produced an intense diabetes in our toads^{103a,b} and maintained it in adrenalectomized dogs with pituitary diabetes.¹¹²

These investigations should be repeated in mammals, keeping them in good condition with cortical extract and salt and injected with active diabetogenic extracts.

One of the strongest arguments in favor of a possible adrenal diabetogenic rôle is that there is frequently hyperglycemia and glycosuria in cases of primitive hyperadrenalism or pituitary basophilism. But in order to interpret these cases one can only put forward the afore-mentioned hypotheses.

Thyroid. Thyroidectomy increases the sensitiveness to insulin (Ducheneau, 1923; Bodanski, 1923) in rabbits^{26, 61, 82, 203} guinea pigs,¹⁰⁹ rats,¹⁰⁹ sheep,¹⁸ dogs^{6, 109, 110} and man;¹³⁰ this has been observed in cases of myxedema.^{14, 183, 197} If the pituitary is removed in a thyroidectomized animal this sensitiveness is increased much more, as has been shown in rabbits (Cope and Marks, 1934) and in normal^{107b} or pancreatectomized⁶ dogs. These experiments all agree excepting those of Britton and Myers (1927) who find the increased sensitiveness is transitory and followed by an increase in resistance. Thyroid treatment increases the resistance of normal or thyroidectomized animals¹⁰⁹ but if it is excessive it decreases it.^{26, 158} The sensitiveness of hypophysectomized rabbits to insulin is not attenuated (Cope and Marks, 1934). In cases of mild diabetes administration of thyroid increases the glycosuria and insulin causes it to disappear (Rosenberg).

Thyroidectomy does not cure diabetes. Wolfson's experiments (1927), and more especially those of Yriart (1930), show that the usual evolution of diabetes after total or subtotal pancreatectomy in the dog¹⁸¹ is neither prevented nor cured by thyroidectomy. In

* Because atrophy of the adrenals occurs in hypophysectomy, removal of the adrenal and pituitary prevent the production of a complete pancreatic diabetes, anterior pituitary extract increases the diabetes in pancreatectomized-hypophysectomized animals but not in pancreatectomized-adrenalectomized animals, adreno-tropic (pure?) extract increases the attenuated diabetes of pancreatectomized-hypophysectomized animals.

† Although it produced it in hypophysectomized-pancreatectomized animals it may not have been sufficiently active or the animals had not a sufficient glycogen reserve.

man, partial thyroidectomy has been ineffectual in treating diabetes, because although total thyroidectomy increases the tolerance to glucose the result does not justify the operation, as it is obtained at the cost of disagreeable symptoms of hypothyroidism (Wilder, Foster and Pemberton^{14,183,197}).

The administration of thyroid does not induce diabetes in normal animals, nor increase the glycosuria of hypophysectomized dogs without pancreas.⁹ In cases of hyperthyroidism it is not rare to find slight hyperglycemia and glycosuria^{117,118,119,153} but true diabetes is not common (average 2.3% according to the numerous statistics compiled by John, 1932, and some others.^{117,118,119,153} Neither is hyperthyroidism common in diabetics (average 1.68% according to John's statistics, 1932). But hyperthyroidism is an unfavorable factor in human diabetes and improvements can be obtained in the latter by subtotal thyroidectomy when both diseases coexist.^{117,118,202}

Sexual Factors. In castrated dogs and bitches we have observed pancreatic diabetes similar to those of normal animals. An increase of the sensitiveness to insulin has been found immediately after the castration,^{44,164} although later a slight increase in insulin resistance can be found.^{165,164}

The influence of pregnancy on pancreatic diabetes has been the object of various investigations which have given conflicting results. The first work was that of Carlson and Drennan. The most recent and valuable is that made by Cuthbert, Ivy and collaborators, in which they give a summary of the pertinent bibliography. Pancreatectomy in bitches at term may not produce hyperglycemia,^{4,30,31,32,52,129} if there are three or more fetuses present in the uterus and there may be hypersensitiveness to insulin.⁵² According to Cuthbert, Ivy and collaborators⁵² in pancreatectomized bitches with uniform diet and insulin and slight glycosuria, pregnancy increases the glycosuria at first and later in advanced stages, the glycosuria is diminished as also the necessary dose of insulin; a greater reduction occurs during lactation. It seems that pregnancy nearing term causes a decrease in blood sugar in some,⁵² though not all the bitches.^{2b,156} It is difficult to decide whether this improvement is due to passage of insulin from the fetus to the mother or to the changes which occur in the pituitary, liver or adrenals during pregnancy.

Cuthbert, Ivy, Isaacs and Gray analyze the clinical aspects in the following phrases "A review of the postinsulin clinical literature on this subject reveals that some report that the pregnancy intensifies and others that it ameliorates the diabetes. Most agree that the state of early pregnancy intensifies or does not change the diabetic condition and that lactation ameliorates it. Kramer¹²⁴ recently on reviewing 110 cases in the literature, found that in late pregnancy the sugar tolerance was impaired in 29%, unchanged in 24 and

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ORIGINAL ARTICLES.

DIABETES AS A DISTURBANCE OF ENDOCRINE REGULATION.*

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THE pathologic changes which bring about diseases are disturbances of the normal functions. For this reason, the knowledge of the physiology of the carbohydrate metabolism is fundamental in order to understand the mechanism of diabetes and to serve as a basis for the purposes of diagnosis and treatment. There is still much to be learned from these basic studies, in which the discovery of insulin, although very important, has been only one step.

The carbohydrate metabolism is regulated by many factors both nervous and humoral, which must be harmoniously coördinated for the existence of integrated function.

Sugar is constantly produced and used. The liver is the essential organ for its production and it is consumed in greater part by the muscles. Various endocrine factors take part in the regulation of the production and consumption, among them the pancreas, pituitary gland, adrenals, thyroids, and gonads. These multiple factors obey a controlling mechanism and so maintain an equilibrium, which is proved by the more or less constant blood sugar level, and the tendency to regain this level if alteration occurs. Denervation of the liver, pancreas, adrenals or thyroids does not manifestly affect the normal level of the blood sugar because the regulation of this endocrine equilibrium is mainly through the blood.

The sympathico-adrenal mechanism, directly or by means of adrenalin, can decompose the liver glycogen, setting free glucose; or by

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means of adrenalin the muscle glycogen is affected, lactic acid being set free which is transformed back to glucose by the liver. This sympathico-adrenal mechanism tends to raise the blood sugar. The pituitary, principally the anterior lobe acts in the same blood sugar raising sense. The thyroid and possibly the adrenal cortex also tend to raise the blood sugar.

On the other hand, insulin secreted by the pancreas tends to lower the blood sugar and prevents it rising above the normal level; it also regulates the consumption and production of glucose.

We will examine the functioning of these factors in their relation to diabetes.

Muscle. According to the studies of my collaborators (Dambrosi, Foglia, Fernández, Biasotti, and others), in dogs and cats glycogen formation is altered in pancreatic diabetes in different progressive steps in the following order: 1, The liver glycogen and its formation from glucose is diminished; 2, after injection of glucose the formation of muscle glycogen is slowed^{72a} (Fig. 3); 3, the re-synthesis after muscular tetanization is slowed and delayed^{53b,d} (Figs. 1 and 2); 4, the basal muscle glycogen is diminished; ^{72a} 5, the cardiac glycogen is generally increased.^{50, 51, 35, 65, 66, 88} Injection of insulin or a pancreatoco-duodenal graft in the neck compensate or over-compensate these deficiencies^{53b,d, 72a} (Figs. 1 and 3). Suprarenal insufficiency produces similar disturbances in the dog, which are compensated by cortin and insulin^{54, 55} (Figs. 13 and 14).

On the other hand, the liver is not necessary for the re-synthesis of muscle glycogen in the presence of insulin. In hepatectomized dogs, Mann and Magath^{152c,d} found the muscle glycogen can fall to half the basal amount. The injection of glucose causes it to rise if the pancreas is present or high doses of insulin are injected.¹⁵⁷ Dambrosi^{53a,e} has shown that the re-synthesis of muscle glycogen after tetanization depends on the level of the blood sugar in hepatectomized dogs; it is good if the blood sugar is high, poor if low. The rôle of the liver is therefore indirect, through its influence on the blood sugar.

The question whether the re-synthesis of the muscle glycogen wasted during tetanization occurs in pancreatectomized animals has been studied and confirmed by some authors^{172, 63, 41, 53a,b, 143, 144} but not by others.^{162, 56a,b, 100, 102} In reality, as has been demonstrated independently by Dambrosi^{53a,b,d} and Lukens, Long and Fry,¹⁴⁴ fatigue causes a decrease in glycogen similar to that in the controls, but there is a slower re-synthesis in the pancreatectomized animals compared with the controls, even though usually the final level is the same; thus there is a marked lengthening in the duration of re-synthesis, but not absence (Figs. 1 and 2). Injection of insulin or pancreatic graft in the neck causes a normal or even more rapid recuperation (Dambrosi^{53a,b}).

The changes in the muscle glycogen which occur on injection of

glucose in pancreatectomized animals have been investigated. Some have not observed any rise,^{37,56a,b,16,103b} others have found this, but in a diminished and slower form.^{149,157} Foglia and Fernández (1933)

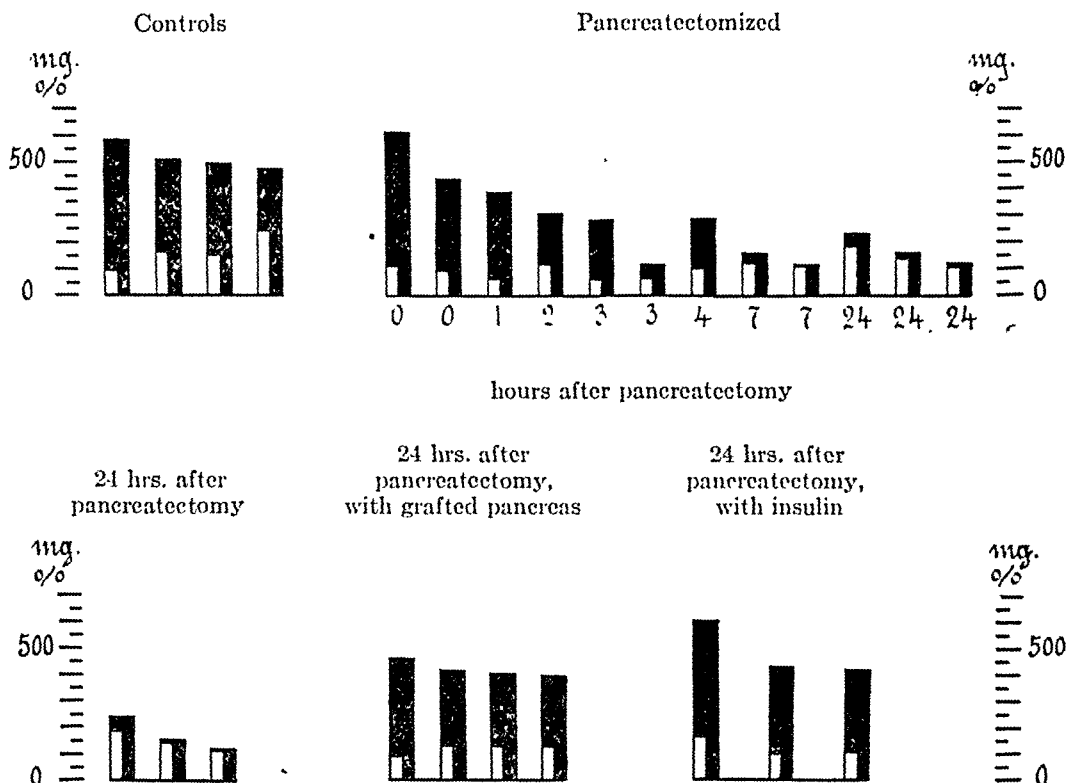


FIG. 1.—Each column represents the average values of muscle glycogen of one dog in mg. per 100 gm. White: immediately after fatigue. Black: after 1 hour rest. (Dambrosi, 1933.)

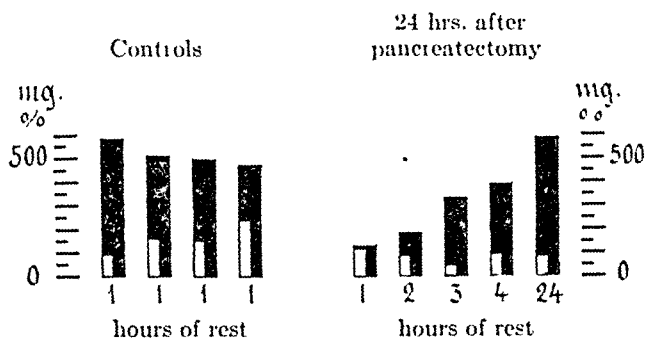


FIG. 2.—Each column corresponds to the average values of muscle glycogen (mg. %) of a dog. Numerals indicate period of rest. White: glycogen immediately after fatigue. Black: glycogen after rest. (Dambrosi, 1933.)

proved that during the first hours following operation, pancreatectomized dogs form glycogen; 5 to 24 hours after the operation glycogen is either not formed or only in very small quantities. If the pancreas is grafted into the neck or insulin injected the forma-

tion becomes normal or super-normal (Fig. 3). This agrees with the known action of insulin which favors the deposit of muscle glycogen in diabetics or normal beings in various conditions.^{71,16,15,47,46,148} For the sake of brevity we will not consider the insulin-sympatico-adrenalin action^{46,36,45} and its influence on the muscle glycogen.

The work of Cruickshank, Evans and collaborators, Himwich and collaborators and Grande may be referred to for data on the consumption of glucose, lactic acid and respiratory quotient of the diabetic muscle and heart.

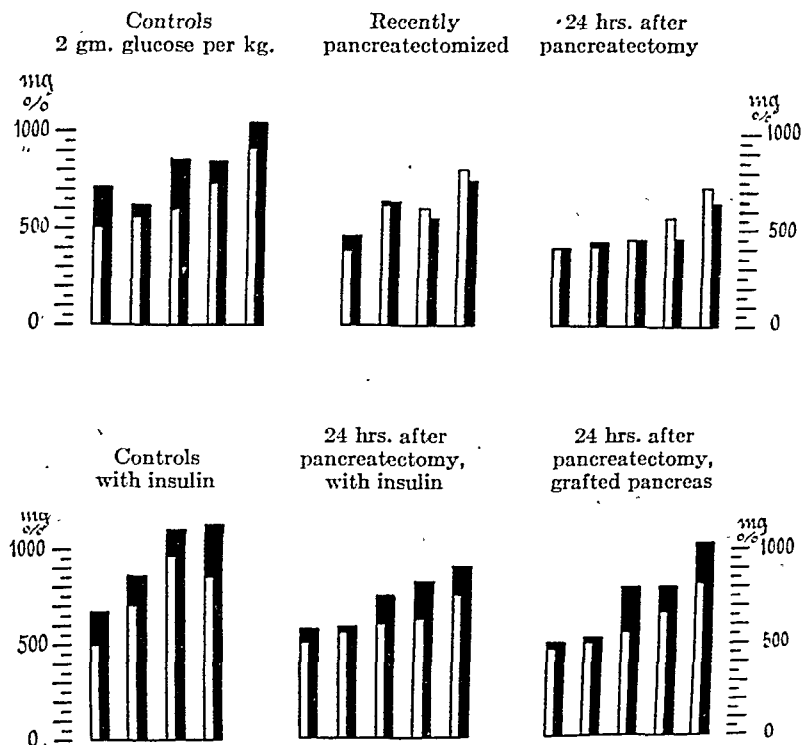


FIG. 3.—Dogs injected with glucose 2 gm. per kg. intravenously. Each column represents the average values of muscle glycogen of one dog in mg. per 100 gm. White: immediately before the injection. Black: one hour after the injection. (Foglia and Fernández, 1933.)

These and other known facts must be interpreted as proof that the muscular metabolism is altered when insulin is lacking. Thus a more intensive study of the metabolic disturbances of the muscle and liver in diabetes may lead us to important discoveries applicable to the treatment of this disease.

Liver. Mann and Magath have shown, and it has been confirmed by ourselves and others,^{152b,c,d,151,199} that the liver is necessary for the maintenance of the normal blood sugar level and for the production of hyperglycemias (diabetic, adrenalinic, asphic-

tic, or anesthetic). Extirpation of the liver causes a rapid fall of blood sugar and when hypoglycemia is reached there are various symptoms which disappear when glucose is administered. If extirpation of the liver is carried out simultaneously with pancreatectomy there is no rise in blood sugar in dogs^{152a,b,c,d} amphibians^{27,164} and birds¹²⁰ and the sugar falls as in simple hepatectomy. If the liver is removed in the dog while there is diabetic hyperglycemia this immediately diminishes reaching hypoglycemia with symptoms which glucose cures (Mann and Magath). If pancreatectomy is carried out after removal of a large part but not all, of the liver, the rise in blood sugar occurs slowly, taking several days (Mann *et al.*).

The presence of the liver is necessary in order that the injection of anterior pituitary lobe can raise the blood sugar to diabetic level in hypophysectomized pancreatectomized toads.²⁷ If the liver is extirpated in a dog with diabetes of pituitary origin, with glycemias of 0.2 to 0.35 gm. %, due to injection of anterior lobe extract, the blood sugar rapidly falls (Houssay and Foglia, unpublished data). From these facts it can be deduced that the liver is absolutely necessary for the production and maintenance of the diabetic action of the pituitary. It is an interesting fact that the blood sugar and muscle glycogen fall less rapidly in hepatectomized toads if they have been implanted with anterior pituitary lobe (Campos, Curutchet and Lanari²⁷).

The presence of the liver is not necessary for the action of insulin. The fall of blood sugar is accelerated in hepatectomized animals (whether the pancreas is present or not) on injection of insulin^{152a,b,161} and glucose improves the hypoglycemic symptoms. Insulin causes an increase in the disappearance of glucose even in decapitated and eviscerated animals.¹⁶

The liver of pancreatectomized animals shows a decrease in quantity of glycogen and after a venous injection of glucose this is either not deposited or in less quantity than in normal liver.^{143,105b}

Pancreas. The internal secretion of the pancreas keeps the blood sugar level normal and corrects or prevents its rise; it allows the liver to form and store normally the hepatic glycogen; accelerates the re-synthesis and storage of muscle glycogen, and allows the normal production and consumption of glucose.

Total extirpation of the pancreas in one or several operations always produces a severe consumptive diabetes which persists during fasting (von Mering and Minkowski, 1889-1892). That this diabetes must be attributed to the suppression of a pancreatic internal secretion, is proved by the following facts: 1, A subcutaneous pancreatic transplantation prevents the diabetes.^{153,97a,b} If the vascular supply is occluded the blood sugar rises but descends again when the ligature is removed.^{95a} 2, If a pancreas (or duodeno-pancreas) is grafted by its artery and vein into the carotid and jugu-

lar of a diabetic dog the blood sugar of the latter descends rapidly to normal, if it is grafted into a recently pancreatectomized dog the blood sugar rise is prevented^{75a,b,76,78,115a} (Fig. 4). This graft causes a rapid disappearance of the disturbance in the formation of hepatic and muscle glycogen in the diabetic dog^{53a,b,72a} (Figs. 1 and 3). 3, If a diabetic dog is injected with the blood from pancreatic veins,^{93c,126a,b,e} its blood sugar falls; this does not occur with injection of blood from the general circulation. 4, Insulin extracted from the pancreas counteracts all the symptoms of pancreatic diabetes and keeps alive for years pancreatectomized dogs suitably fed.^{93c,34}

The pancreas secretes insulin continuously. After pancreatectomy there is a definite rise in blood sugar in from 2 to 4 hours^{94,115a} which continues from 1 to 2 days and then remains stationary. With Lewis and Foglia we found that in order to keep the blood sugar normal in a pancreatectomized dog, insulin must be injected continuously in a dosage of about 0.01 unit per kg. per hour, the extreme limits being 0.005 and 0.02 unit per kg. per hour.^{105,115c,90}

Rise in blood sugar stimulates the pancreatic endocrine function and increases the secretion of insulin;^{187,126a,b,c,87,86,75a,b,115a,138,8,68,72c} our experiments with Lewis and Foglia (1928) allow us to conclude that variations in the secretion of insulin are important and can go from 10 to 1. An excessive administration of sugar may exhaust and damage the pancreas and increase the severity of Sandmeyer's diabetes, as we have seen together with many experimenters since Allen.^{2a}

On the contrary the hypoglycemias induced by insulin,^{204a} synthalin^{204b} and hepatectomy^{204c} cause a decrease in the secretion of insulin.

Further, as intense and prolonged administration of gonad hormones can cause atrophy of the gonads and those of the thyroid atrophy of the thyroid gland, so does the administration of insulin inhibit the secretion of insulin. Even though it can give rise to an increase in number and volume of the islet cells and their insulin content¹²⁸ it ends by inhibiting their proliferation¹⁴⁶ activity and secretion and when the insulin is no longer administered in normal animals, the hyperglycemic curve produced by glucose is lengthened¹⁹³ and spontaneous hyperglycemias and glycosurias are observed for some time.^{193,170,171}

The pancreas regulates the normal level of the blood sugar preventing hyperglycemia and in its turn the normal blood sugar keeps the internal secretion of the pancreas normal, increasing it if there is hyperglycemia and diminishing it when there is hypoglycemia; thus there is a reciprocal mechanism.

The pancreas, through insulin, allows the normal and rapid formation of glycogen. This pancreatic endocrine regulation is maintained in order essentially by humoral factors, with certain accessory nervous factors.

There has been much discussion whether the internal secretion of the pancreas is governed by the central nervous system or by changes in the blood. Our experiments have shown that the humoral mechanism is preponderant and that the nervous one is secondary and can be dispensed with, but it helps to integrate with more rapidity and perfection the pancreatic endocrine secretion.

After section of the vagus nerves the blood sugar is maintained within normal limits (Etcheverry)^{141,140} although sometimes slightly lower figures have been observed^{40,178,80} or even slightly raised ones.^{21,115a,73} Observations contrary to this statement made by La Barre (1927-1928) can be attributed to inappropriate technique; it is convenient to do the experiments over a long interval with well-fed unanesthetized animals. We have, together with all other experimenters, found that denervation of the pancreas *in situ*^{93b,137,2c} does not produce diabetes, neither does denervation of a transplanted pancreas nor part of the pancreas.^{7a,93b}

The curve of sugar tolerance is only slightly affected by section, either uni- or bilateral, of the vagus. The fall of blood sugar after administration of glucose has been studied by various observers^{7a,176,104,173} who found it the same as in normals, although Gayet^{75b,77a} found a slightly quicker fall and Clark⁴⁰ found a transitory initial increase and later a prolonged fall. We found with Lewis and Foglia in 1928, that there was a slower fall in all dogs^{115a,73} with vagi cut or denervated grafts (Fig. 9). Etcheverry has investigated this point very thoroughly and has found that without exception in every dog observed before and after bilateral supradiaphragmatic vagotomy or denervation of the pancreas, there is lengthening of the fall in blood sugar, a disturbance which is noted for several weeks but which slowly decreases. On the other hand, there is no such change when the liver is denervated (Fig. 9) or other operations carried out. The vagi therefore have some influence, though it is accessory and not indispensable. The regulation of the secretion of insulin (without vagal intervention) during hyperglycemia has been shown by other experiments.^{43,174}

The affirmation made by Hoet and Ernould, Hoet, Debois, that the vagi are necessary for the secretion of insulin, because vagotomy prevents the formation of muscle glycogen, is inexact, and probably due to faults in technique, such as anesthesia or asphyxia. In reality, vagotomized dogs and cats re-synthesize muscle glycogen after fatigue (Dambrosi, 1933) (Fig. 7) and store it after injection of glucose just as the controls (Foglia and Fernández, 1933; Long and Fry, 1933).

Various experimenters have noted a decrease in the blood sugar on vagal stimulation^{48,145,185,21,103,126a,175a,89} which is usually slight and not constant and of little significance. La Barre and Vesselowsky (1933) have observed this decrease in cats which have been adrenalectomized and the hepatic nerves cut, to avoid their action on the

liver and the antagonistic action of adrenalin. Gayet^{75b, 77a} however has not obtained a decrease under any experimental conditions. Etcheverry has repeated the experiments of La Barre and Vesselow-sky with better technique, stimulating supradiaphragmatically both vagi in chloralosed dogs in which in separate and successive operations the left adrenal medulla, the right adrenal, the nerves of the liver, the major and minor splanchnics and the abdominal sympathetic chains had been removed; but in no case, in spite of the excellent condition of the animals, which did not suffer from cortico-adrenal insufficiency as did those of La Barre, has there been hypoglycemia.

Zunz and La Barre in many papers uphold the theory that the secretion of insulin is governed by the central nervous system. In order to detect the secretion of insulin they use a pancreatico-jugular anastomosis, passing the pancreatic venous blood of one dog into the jugular of another, which is usually diabetic due to pancreatectomy and in which the suprarenals have been extirpated so that the insulin will not be able to stimulate a hypersecretion of adrenalin capable of counteracting the hypoglycemia. Those reactions which take place in the donor and which are suppressed on vagal section or atropinization, can be considered as of central nervous origin and transmitted by the vagi. In some experiments the donor dog is decapitated, leaving the vagus nerves intact, uniting the head which is irrigated by the blood of another dog, thus an agent can be observed at will either on the head or the trunk.

Using this technique it can be seen that hyperglycemia of the head brings about an increase in pancreatic secretion due to stimulation of the central nervous system which is transmitted through the vagi.^{204d} Hypoglycemia in the head which may have been brought about by insulin,^{204a} synthalin^{204b} or hepatectomy^{204c} causes an inhibition of the secretion of insulin. As for the localization of the controlling centers for the secretion of insulin or the blood sugar level, according to Brugsch, Dresel and Lewy²⁵ these are to be found in the nucleus of the vagus, according to La Barre^{126c} in the thalamic region and in the pons according to Donhoffer and Macleod.⁵⁸ Puche Alvarez^{175b} using the same technique as Zunz and La Barre has found that asphyxia causes an increase in the secretion of insulin; on the other hand Gayet,^{75b, 77a} with the same technique and also improved experiments, denies emphatically that the secretion of insulin is influenced through central stimulation by glucose.

Zunz and La Barre maintain that adrenalin,^{204e} posterior pituitary extract,^{204f} anterior pituitary pancreatotrophic substance²⁰⁴ⁱ and large dose of thyroxin^{204b, g} stimulate the pancreas directly, increasing its secretion of insulin. Other substances or agents increase the secretion of adrenalin and this in its turn stimulates that of insulin; thyroxin^{204g} ultraviolet rays, amino acids,^{126f} etc., are in this category. Moreover, the thyrotropic hormone stimulates the thyroid secretion,

which in its turn provokes insulin secretion.^{204b} Work done on the pharmacologic influence of various agents on the secretion of insulin has been summarized by Foglia in his thesis 1931, and La Barre in his book 1933.

The method of grafting the pancreas into the neck has furnished many proofs in favor of the fact that the regulation is essentially humoral. The duodenum and pancreas of one dog is taken out and united by its artery to the carotid and its vein to the jugular of another dog. Similar results are obtained if the pancreas alone is grafted in this way but it is easier to graft the duodeno-pancreas preparation and its survival is more certain. A pancreas thus grafted can be kept alive in perfect condition for 10 to 15 hours. The graft has a specific action on the blood sugar which is not shown by grafts

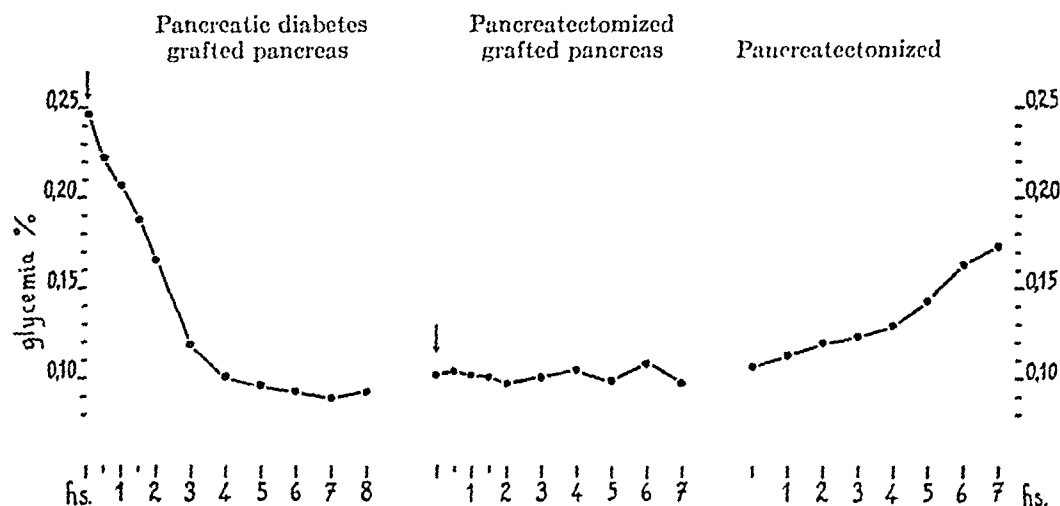


FIG. 4.—Composite curves of glycemia of chloralosed dogs. Pancreatic diabetes (3 dogs); arrow: pancreas grafted in the neck. Pancreatectomized (4 dogs) and immediately after (arrow) graft of pancreas in the neck. Pancreatectomized (5 dogs). (Houssay, Lewis and Foglia, 1928.)

of duodenum alone or of kidney. It plays the same rôle as the pancreas *in situ*, keeping the blood sugar within normal limits and preventing its rise, responding to stimulation through the blood stream with a changing and regulated discharge of insulin. This preparation has been used by Gayet and Guillaumie,^{76,78} Houssay, Lewis and Foglia,^{115a,b} La Barre,^{126b} Dambrosi,^{53a,b} and Foglia and Fernández.^{72a,c}

In the presence of this graft the rise in blood sugar in dogs due to pancreatectomy does not occur^{75a,b,76,115a} (Fig. 4). If it is grafted into a dog suffering from pancreatic diabetes the blood sugar falls to normal levels in 2 to 3 hours and remains stationary (Fig. 4); if the graft is removed the blood sugar rises again.^{75a,76} In order to obtain a similar curve of the fall in blood sugar in a pancreatectomized animal it is necessary to inject by continuous per-

fusion 10 times the basal quantity of insulin and continue lessening it as the blood sugar descends, that is to say varying the dose from 10 to 1 (Houssay, Lewis and Foglia, 1928).

If one, two or even three extra pancreases are grafted into a dog the blood sugar remains normal, showing that the four pancreases together act as one, since their secretion is decreased and adjusted according to the level of the blood sugar (Gayet,^{75a,76} Houssay, Lewis and Foglia^{115a,b}) (Fig. 5).

If glucose is injected into a pancreatectomized dog which has a pancreatic graft in the neck, the blood sugar curve obtained is almost the same as normal (Gayet,^{75a,76} Houssay, Lewis and Foglia^{115a}) there being slight differences which will be discussed later.

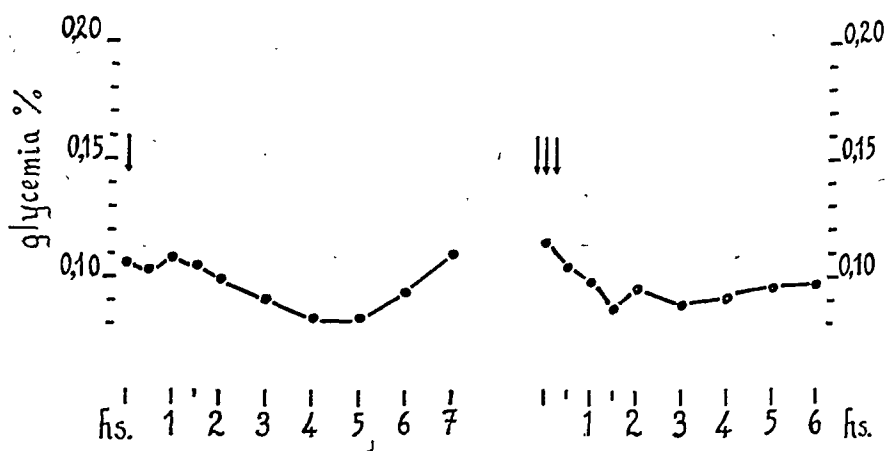


FIG. 5.—Composite curves of glycemia of chloralosed normal dogs. One arrow, graft of one pancreas in the neck (5 dogs). Three arrows, graft of three pancreases (2 dogs). (Houssay, Lewis and Foglia, 1928.)

Injection of glucose into the pancreatic artery causes an increase in the secretion of insulin and a transitory fall in the blood sugar; this may be seen with the pancreas *in situ* (Grafe and Meythaler,^{87,86} Kosaka,¹²³) or with the pancreatic graft in the neck according to Gayet^{75a,b,77b} and Foglia and Fernández^{72c} (Fig. 8).*

The grafting of a pancreas in the neck of a diabetic dog corrects the disturbances in the re-synthesis of glycogen during fatigue (Dambrosi^{53b}) and helps the storage of muscle glycogen after injection of glucose (Foglia and Fernández^{72a}).

We hold that the regulation of the secretion of insulin is essentially a humoral mechanism because: 1, Denervation of the pancreas *in situ* hardly affects the blood sugar and only slightly the sugar tolerance curve. 2, The pancreas grafted into the neck functions normally without extrinsic nerves.†

* Houssay and Lewis^{115b} and La Barre^{126b} could not demonstrate this before.

† We have no data on the possible rôle of the intrinsic innervation.

Nevertheless the nervous system does play some part in the dog* although it is secondary, accessory and can be dispensed with. We

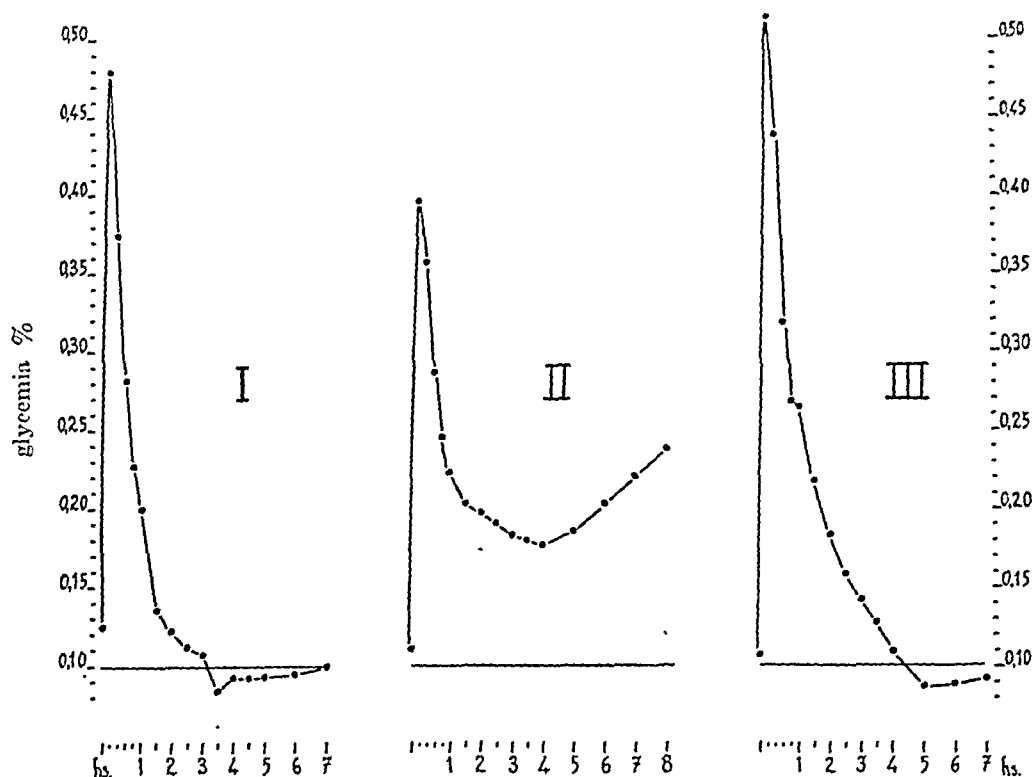


FIG. 6.—Composite curves of glycemia of chloralosed dogs injected intravenously with 1 gm or glucose per kg. I = 6 normal dogs. II = 5 dogs immediately after the pancreatectomy. III = 6 dogs pancreatectomized, with pancreas grafted in the neck. (Houssay, Lewis and Foglia, 1928.)

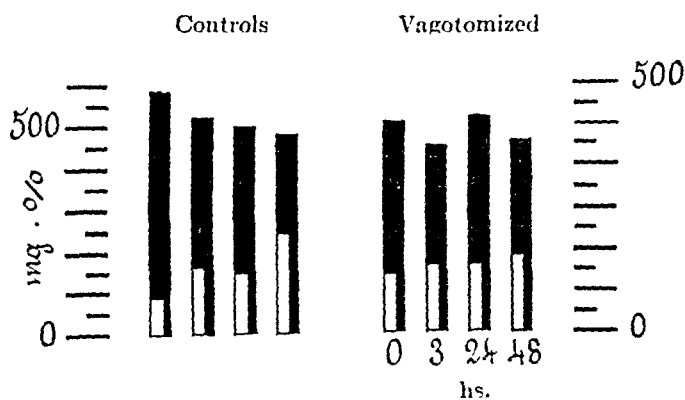


FIG. 7.—Each column represents the average of the muscle glycogen (mg. %) of a chloralosed dog. White: immediately after the tetanization. Black: after one hour of rest. (Dambrosi, 1933.)

* The animal which has served for all our studies.

base this affirmation on the following facts elicited in our Institute.*
 1, When the pancreas is denervated† after venous injection of glucose the fall in the blood sugar curve is, in the dog, always slower than when the pancreatic innervation is intact (Fig. 9). 2, When insulin is injected the rise in blood sugar in animals with a denervated pancreas† is slower than if the pancreas is intact (Fig. 9).

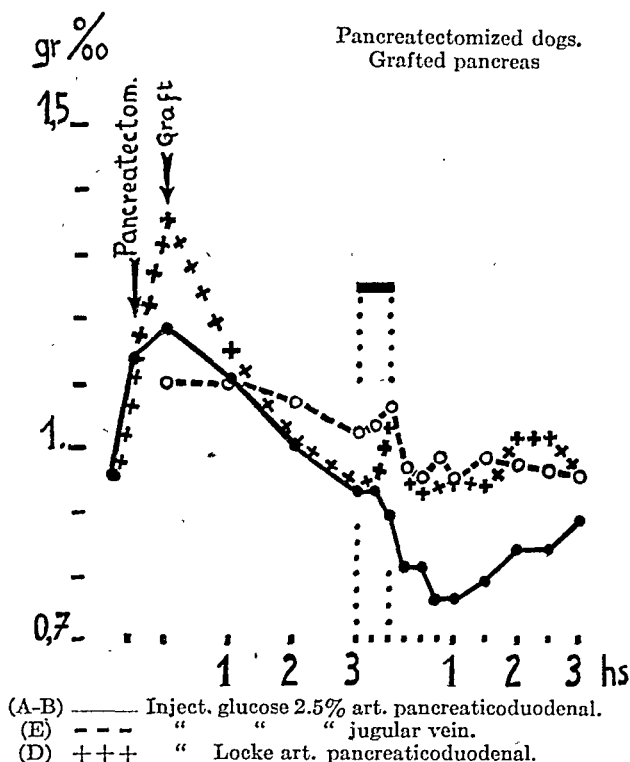


FIG. 8.—Averages of 10 dogs (A. B.), 8 dogs (E) and 6 dogs (D). The upper black mark indicates the time of injection. (Foglia and Fernández, 1935.)

These facts show that the vagus is coöperating with the humoral regulation, increasing the secretion of insulin during hyperglycemia thus accelerating recuperation, and decreasing the secretion during hypoglycemia, thus helping the return to normal. That is to say the secretion of insulin is governed by a complex mechanism which is fundamentally humoral but which is aided by the nervous system through the vagus.

The pancreas maintains the normal level of the blood sugar inhibiting hyperglycemia, but in its turn the normal blood sugar

* To which experiments can be added those of Zunz and La Barre, Puche Alvarez and others which we have not attempted to confirm.

† By section of the vagi or pancreatic nerves, or in the case of the pancreatic graft.

regulates the normal internal secretion of the pancreas which is stimulated by hyperglycemia and inhibited by hypoglycemia. Therefore the blood sugar level regulates the secretion of insulin.

In certain pathologic cases the normal regulatory mechanism is altered, especially in cases of islet adenoma (or even simple hyperplasia) when hyperinsulinism is present. This type of secretory alteration and hyperfunction is seen in adenomas of other glands, namely thyroid, pituitary, parathyroids and adrenals.

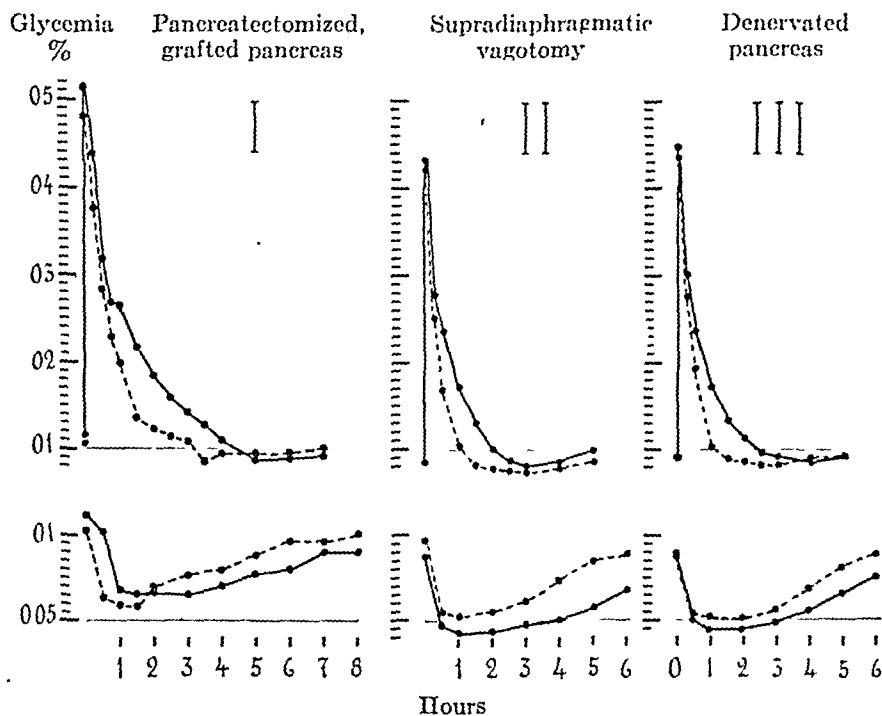


FIG. 9.—Above: Average glycemic curves of dogs injected intravenously (jugular) with 1 gr. glucose. Below: Average glycemic curves of dogs injected intravenously (jugular) with 3 U. insulin.

I ——— 6 pancreatectomized dogs, anesthetized with chloralose, and with pancreas grafted.

----- 6 control dogs. (Houssay, Lewis and Foglia, 1928-1929).

II ——— 12 vagotomized dogs, not anesthetized.

----- 12 controls (Etcheverry, unpublished).

III ——— 6 dogs with denervated pancreas, not anesthetized.

----- 6 controls. (Etcheverry (unpublished)).

Although frequent changes in the pancreas and islets are found in diabetic patients, pathologists agree that there is no specific lesion of the pancreas in diabetes.^{96,116} The functional disturbance probably has a preponderant importance in the development of the symptoms. The impossibility of measuring accurately the insulin circulating in the blood prevents the knowledge of whether or not it is decreased in diabetics. Or, if the insulin circulating in the blood is normal or raised, whether the organism requires more than is secreted, or else is insulin-resistant. In any case, the diabetic

pancreas does not respond with a sufficient secretion to correct the hyperglycemia. The insulin secretory mechanism is altered.

Whatever the concentration of insulin, low, normal or raised, it is insufficient for the necessities of the organism. The proof of this is that injections of insulin bring about the disappearance of the diabetic symptoms. Therefore the pancreas does not produce a sufficient quantity of insulin for the necessities of the diabetic organism.

In time a more perfect knowledge of this regulation of the secretion of insulin will probably guide us in the diet and treatment of diabetes. I think it is a field well worthy of further exploration.

Pituitary. We will make only a brief summary of the principal known facts on the influence of the pituitary gland in diabetes (a subject which has been studied extensively in our Institute since 1929), since one of the Dunham lectures which I gave at Harvard, in 1935, was on the pituitary and carbohydrate metabolism and can be referred to for further data.^{107b}

Serious disturbances in the carbohydrate metabolism are caused by lack of the pituitary or the glandular lobe of the pituitary. Injection of extract of this lobe counteracts or produces the opposite symptoms. The neuro-intermediate lobe also possesses some of these corrective actions, though not all and to a lesser degree.

During pituitary insufficiency, fasting and different hypoglycemic agents readily provoke severe or even fatal hypoglycemic crises if treatment with sugar is not started in time. There is a marked sensitiveness to insulin. Most, though not all, experimental hyperglycemias are less marked than in the controls.

Glycogen diminishes in fasting and it is more difficult to keep it high.^{108b*} There is an exaggerated glycogenolysis during fasting though this usually is less rapid than in the controls after injection of adrenalin, insulin, or pilocarpin, or in asphyxia, etc.

We have shown with Biasotti (1929-1930 and later) that in the absence of the pituitary or its glandular lobe there is an attenuation of pancreatic diabetes. There is longer survival, wounds will heal, the fall in weight and azoturia are lower, the hyperglycemia and glycosuria are less, ketonemia and ketonuria scanty, the basal metabolism is little or not raised at all, the lipemia and cholesterolemia are less marked and the dextrose-nitrogen ratio is low; severe spontaneous hypoglycemic crises occur and there is increased sensitiveness to insulin, both being cured with the administration of sugar. If sugar is injected intravenously it is partially or totally retained. The respiratory quotient frequently rises, sometimes as in normal animals, the fall of the blood sugar curve is longer than in normals but more rapid than in diabetics. Daily administration of sugar increases the severity of the diabetes.

These experiments prove: 1, The presence of the anterior pitui-

* In asthenic toads the re-synthesis occurs with delay (Dambrosi, unpublished work).

tary lobe is a factor which increases pancreatic diabetes. 2, Hypophysectomized animals without the pancreas and therefore with no secretion of insulin can utilize and consume sugar, that is to say, the pituitary causes a decrease in the utilization of sugar in the diabetic.

When there is no pituitary gland, phloridzin diabetes is less marked. There is a rapid and fatal hypoglycemia in fasting, which is counteracted by the intake of protein or sugar, but not by fat. There is less glycosuria, ketonuria, azoturia and the dextrose-nitrogen ratio is low. The administration of anterior pituitary lobe extract increases this attenuated phloridzin diabetes of hypophysectomized animals.

The following effects of pituitary extracts have been described:^{3b,c} a blood sugar raising action of extract of the posterior lobe, pancreatotropic (Anselmino, Herold and Hoffmann), contrainsular (Lucke), glycogenolytic (Kohleydratstoffwechselhormon of Anselmino and Hoffmann), diabetogenic (Houssay and collaborators) and also a blood sugar raising substance which has a rapid action, is ultrafiltrable and active without the presence of the adrenals (Anselmino and Hoffmann).

I agree with Anselmino and Hoffmann that the work of Lucke has been given too much importance, possibly because of the number of his papers and the well-sounding though inappropriate name, contrainsular hormone, which he has used. The commercial extract he has used has an immediate, though faint, inconstant and transitory, blood sugar raising effect; it has the same characteristics as the extract of posterior lobe, that is to say, they do not occur in the absence of adrenals or the liver. Also it is not diabetogenic in the normal animal.

We have increased the attenuated pancreatic or phloridzin diabetes of hypophysectomized animals with alkaline extracts of the anterior lobe injected into the peritoneal cavity. The organism becomes insulin resistant. Diabetes can be induced in normal animals.

With daily injections of this extract in normal dogs the blood sugar rises in 2 to 3 days to level of 0.15–0.35 gm. % where it remains several days. This hyperglycemia of anterior pituitary diabetes may be termed alimentary since it only occurs in normally fed animals, being more rapid and intense if they are given carbohydrates and does not occur or only slightly so if the animals are fasting. There is no increase in blood sugar the first day, but this occurs the second or third day and persists all day with oscillations. If the anterior pituitary extract is omitted the blood sugar falls to normal in 2 to 3 days. During the anterior pituitary diabetic hyperglycemia there is ketonemia and ketonuria (though much less than in pancreatic diabetes), glycosuria, hyperlipemia and hypercholesterolemia and an increase in the hepatic glycogen. If glucose is injected into the veins it is partly or sometimes totally eliminated;

the hyperglycemic curve is prolonged as in diabetes. The respiratory quotient may remain unchanged. Even if hyperglycemia does not occur, the glycemic curve is of diabetic type and there is a strong resistance to insulin.

The anterior pituitary diabetogenic action can be seen in hypophysectomized pancreatectomized toads even when the gonads, thyroids, digestive tract or lungs, kidneys, anterior or intermediate brain, or adrenals^{108b, 112} have been removed. It is also seen in dogs which have been castrated, or thyroidectomized, hypophysectomized, or with denervated adrenals, or with the adrenal medulla removed, or where there has been bilateral supradiaphragmatic vagotomy, or extirpation of the abdominal sympathetic chain and section of the major and minor splanchnic nerves.

The liver is necessary for the diabetogenic action of the anterior pituitary extract in the hypophysectomized pancreatectomized toad (Campos, Curutchet and Lanari²⁷). Hepatectomy causes the raised blood sugar of the anterior pituitary diabetes in dogs to fall rapidly to hypoglycemic levels (Houssay and Foglia, 1936).

We have shown with Biasotti^{108a, b} and Leloir¹¹² that in the toad species *Bufo arenarum* the presence of the adrenal is not necessary. Pancreatic diabetes in the toad can be diminished by: 1, hypophysectomy (or removal of the glandular lobe of the pituitary); 2, adrenalectomy; 3, extirpation of both these glands.

In these 3 cases injection of glandular lobe of the pituitary causes a reappearance of the diabetic hyperglycemia in all its intensity; on the other hand, injection of cortin or adrenal extract does not alter the blood sugar (see table).

These results differ from the very important results obtained by Long and Lukens^{139, 141} in the cat. They found that pancreatic diabetes is diminished by hypophysectomy or adrenalectomy. Cortin does not increase the blood sugar. Anterior pituitary extract increases the blood sugar in hypophysectomized-pancreatectomized animals but not in the adrenalectomized-pancreatectomized. For this reason they suppose that the anterior pituitary extract produces its action through the adrenals.

I think that before believing these phenomena are different in amphibians and mammals it would be better to repeat the experiments, injecting with a powerful diabetogenic extract, adrenalectomized mammals which are kept in good condition by salt treatment and whose glycogen is high.

We have studied with Foglia particularly the relationship of anterior pituitary diabetes to the endocrine function of the pancreas. Anterior pituitary extract has an extrapancreatic diabetogenic action, since it can bring about a considerable hyperglycemia and increase the diabetes in hypophysectomized-pancreatectomized animals. In normal dogs the injection of this extract can also produce an insulin resistance which can be shown in three ways: 1,

improved in 47% of patients. Hypertrophy and hyperplastic islets have been observed in several infants born of diabetic mothers^{85,89,169} and hypoglycemic symptoms in such infants have also been observed.¹⁷⁷ In an especially valuable article written by White in Joslin's book¹¹⁸ she points out that there is no significant increase in tolerance.

With the idea of inhibiting the action of the anterior pituitary lobe, the influence of injections of estrin on pancreatic diabetes and the sensitiveness to insulin has been tried (Barnes, Regan, Nelson, etc.). Treatment with estrin, before or after pancreatectomy, causes marked improvement in the hyperglycemia and glycosuria with longer survivals in dogs^{10,12} and monkeys.^{166,165} In human diabetes, favorable results have also been reported,^{17,107b,160,186} but also no results.⁴²

Summary. Diabetes is a disturbance of the carbohydrate metabolism in which the normal balance of the regulating factors is altered.

The muscular disturbances are secondary to functional changes in the liver and hormones (insulin, pituitary, adrenals).

In this regulation the liver holds the most important part, since it is the organ which produces glucose and thus governs the blood sugar under the influence of the hormone equilibrium. If the liver is absent, diabetic hyperglycemia cannot occur.

The production of each hormone is regulated and there is a reciprocal equilibrium between them.

The endocrine secretion of the pancreas has a fundamental rôle, since it maintains the blood sugar at normal level and prevents its increase and influences the production and consumption of glucose. The secretion of insulin is governed by the level of the blood sugar and *vice versa*. The central nervous system is not necessary for the normal secretion of insulin but comes into play if there are changes in the blood sugar. The vagus has only a secondary and accessory rôle causing a more rapid and perfect regulation in these cases.

The presence of the anterior pituitary prevents hypoglycemia and the decrease in glycogen during fasting, diminishes the action of hypoglycemic agents and is necessary for the development of diabetes in all its intensity. An excess of anterior pituitary secretion increases the diabetes or even will bring about a diabetic state (even when the adrenals, thyroid or pituitary is absent). It greatly increases the resistance to insulin even when the pancreas is absent and causes a decrease in the endocrine secretion of the pancreas.

The adrenals have many actions. The sympathetic adrenal function is antagonistic to insulin. The lack of adrenal cortex brings about a gradual hypoglycemia with decreased storage and re-synthesis of glycogen and amelioration of the pancreatic diabetes. Cortin corrects the blood sugar level and glycogen, but is not diabetogenic. The possible diabetogenic action which is an explana-

tion of the hyperglycemias found in cases of hyperinterrenalism has not been proved.

The thyroid favors the destruction of glycogen and decreases its formation.

The sexual hormones and the pregnant state can influence diabetes, possibly through the pituitary or liver or adrenals.

An imperfect but suggestive conception of the diabetic state can be arrived at by considering the pancreas as an antidiabetic factor and the anterior pituitary, adrenals and thyroid as diabetogenic or diabetes stimulating factors.

In all diabetes there is an insufficiency of insulin in relation to the needs of the organism, the actual secretion itself may be normal or increased. There is also an imperfect regulation of the endocrine secretion, since it cannot adjust itself to the needs of the organism in order to bring about a normal blood sugar level.

In all diabetes there must surely be an anterior-pituitary factor, since this secretion, either normal or increased, augments diabetes. With similar reasoning one may suppose that the other glands (adrenals, thyroid and gonads) play a part in all diabetic states, either directly because of their specific function or through their influence on other organs. The importance of these actions has not yet been defined.

The various forms of experimental diabetes are due to the destruction of the normal equilibrium of all these factors. With time it is to be hoped it will be possible to establish what equilibrium exists in the various forms of diabetes, hyperglycemias and glycosurias met with in human diseases. This knowledge should give us a firmer basis for the exact diagnosis and treatment of these cases.

It has been necessary to omit the extensive bibliography of this article; however, it will be included in the reprints for which requests can be forwarded to the author.

OBSERVATIONS ON PROTAMINE ZINC INSULIN.

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SINCE the publication of the earlier report on protamine insulin from this clinic there has been a marked improvement in the product. At that time it was not stable after the insulin and protamine buffer were mixed, and as a consequence was usable for only a short time. The addition of calcium or zinc to the preparation increased its stability. Now the insulin and the protamine buffer with zinc are mixed at the time of making, and this product is stable for a period of about 6 months. The earlier preparations

seemed to exert a hypoglycemic influence for from 12 to 16 hours. This necessitated, in many patients who require a considerable number of units per day, the use of a second dose in order to control the blood sugar during the entire 24 hours. The combination of two injections of insulin during the day resulted in a double absorption often difficult to control from day to day. Hypoglycemic reactions, while not common, did appear to occur when the absorption of the two areas was not constant.

The effectiveness of the mixed protamine zinc insulin has been increased, so that it is at present active for a period of 24 hours after taking. This is shown by the occurrence of hypoglycemic reactions 24 hours after the dose has been taken. It is thus evident that the use of this preparation of insulin consists in giving, before breakfast, an amount sufficient for 24 hours, and so adjusting the food intake that neither hyperglycemia nor hypoglycemia occur. In this way we approach as nearly as may be to the action of insulin as it is supposed to be in the normal individual. In a few patients requiring excessive amounts of insulin it may be advisable to make the adjustment on two doses daily.

Transfer to Protamine Zinc Insulin. The longer time during which protamine zinc insulin is effective in the body makes it possible to adjust the patient on one injection daily. This single injection is active for the full 24 hours. Insulin, on account of its short period of activity, is adjusted to the meals. Protamine zinc insulin, however, may be given once daily and the food adjusted to it. The greater convenience to the patient, as well as the more satisfactory balance which can be maintained between the absorption of both the one dose of protamine zinc insulin and the food, make this perhaps the most satisfactory method of controlling the metabolism of the diabetic.

The action of protamine zinc insulin is delayed so that the period of greatest effectiveness often occurs 12 or more hours after its administration. Furthermore, a definitely increasing activity is usually found for from several days to a week or more, so that the dose should not be increased until it is evident that the maximum effect has been obtained with the amount then being given. In starting the use of protamine zinc insulin four groups of patients may be recognized, namely: 1, those patients who have been taking a single dose of insulin daily; 2, those with two or more doses daily; 3, those who, while not taking any insulin, have only a trace of sugar during part of the day; and 4, those patients who, whether or not they have taken insulin in the past, are entirely out of adjustment and must be balanced anew on diet and insulin.

1. Those patients who are sugar free with an adequate diet and one dose of insulin daily may be transferred to protamine zinc insulin by giving, 1 hour before breakfast, two-thirds the number of units of insulin previously used. With this should be given a

rearrangement of diet which we have called for convenience the "protamine diet," and which will be discussed later. Only a slight alteration in the amount of protamine zinc insulin or in the distribution of the diet will usually be necessary in order to continue these patients in satisfactory adjustment. The blood sugar will then be found to be relatively constant throughout the day.

2. Patients who are taking two or more doses of insulin daily with an adequate diet may be transferred to protamine zinc insulin with little more difficulty than those of the previous group. In order to have the blood sugar as nearly normal as possible in the morning of the day on which the change is to be made, it is well to give, before supper the previous evening, a dose of protamine zinc insulin equal to two-thirds the amount of insulin regularly used at that time. This may be followed, before retiring, by a small amount of slowly absorbing food such as $\frac{1}{2}$ glass of milk with two saltine crackers containing about 10 gm. of carbohydrate. This will prevent any hypoglycemia during the night. On the following morning, 1 hour before breakfast, there is given a dose of protamine zinc insulin equal to two-thirds the total number of insulin units previously given during the 24 hours. After several days, during which the "protamine diet" is used, some alteration in the distribution of the food and in the number of units given will insure satisfactory adjustment. Several days should elapse between changes in the dose of the protamine zinc insulin, because the effect of an increase or decrease is not immediately evident.

3. Some patients who are almost sugar free on an adequate diet may be brought into complete adjustment by the use of 5 or 10 units of protamine zinc insulin given from $\frac{1}{2}$ to 1 hour before breakfast. With these patients it is often not necessary to alter the arrangement of the diet in any way.

4. Patients who are completely out of balance may be given protamine zinc insulin immediately if desired. However, on account of its delayed action and cumulative effect, it is probably more satisfactory at present to adjust these patients on diet with one or more doses of insulin, transferring them later to protamine zinc insulin as described above.

All of these changes can be made without hospitalization if care is used, and if the patient is under frequent observation.

Diet. Dietary care is fully as necessary with protamine zinc insulin as with insulin. A diet composed of 1 gm. of protein per kilo of body weight, an amount of fat equal to or slightly less than that found in the diet of the non-diabetic (80 to 100 gm. daily) and an amount of carbohydrate sufficient to provide the requisite number of calories daily, will be found very satisfactory. An adequate diet should maintain the normal weight and strength of the patient at an optimum level. The rearrangement of the daily food intake, which we have called the "protamine diet" is made as follows: 25 gm. of carbohydrate, reserved from the total daily intake, is

distributed as 5 gm. of starch between breakfast and lunch, and 5 gm. between lunch and supper. The remaining 15 gm. is given before retiring in the form of crackers and milk, so that hypoglycemia during the night is prevented. The remainder of the carbohydrate, together with the protein and fat, is then distributed among the three meals so that $\frac{1}{5}$ of the food is given at breakfast and $\frac{2}{5}$ at each of the other two meals. The morning and afternoon crackers, the later supper before retiring, and the distribution of food as described among the three regular meals all aid in preventing excessive hyper- or hypoglycemia. Some patients, after adjustment, may discontinue the use of the morning and afternoon crackers, though it is probably better to continue the late supper, especially if the regular supper is taken early. Otherwise there is too long a period without food between supper and breakfast.

Urine Examinations. In order to check the balance between the protamine zinc insulin and the food, 4 urine specimens may be collected, namely: 1, 7 A.M. to 11 A.M.; 2, 11 A.M. to 4 P.M.; 3, 4 P.M. to 9 P.M.; 4, 9 P.M. to 7 A.M. If these specimens cannot be procured *in toto*, individual specimens taken at 11 A.M., 4 P.M., 9 P.M. and 7 A.M. will suffice to give the desired information regarding the balance of the insulin and food throughout the day. Alteration of the amount of the protamine zinc insulin or of the amount or distribution of the food will bring about a satisfactory adjustment, and must, of course, be based on the results obtained in each individual case.

Blood Sugar Determinations. Blood-sugar determinations need not be made until the urine contains no sugar, when a specimen of blood should be taken to determine, if possible, whether there is present a renal threshold above 180 mg. If a renal threshold higher than this is found, urine examinations cannot be depended upon to maintain a satisfactory adjustment. When all specimens of urine are sugar free further blood-sugar determinations should be made from time to time in order to ascertain whether the blood sugar is too close to the hypoglycemic level (60 to 70 mg.) or too close to the hyperglycemic level (160 to 170 mg.).

Hypoglycemic Reactions. Hypoglycemic reactions may occur following protamine zinc insulin, but are less frequent and usually less severe than after insulin. They may appear at any time during the day or night, though they are most frequent at from 12 to 24 hours after the injection. Their onset is slow and insidious as compared with those following insulin. This delay in their development, however, affords sufficient opportunity to initiate treatment if the patient will but observe their approach. The slower action of the protamine zinc insulin frequently makes the reactions of longer duration so that they may be expected to recur at short intervals after being relieved by sugar. Except for one reaction which occurred early in our experience and which was very severe, we have not found any difficulty in controlling them with sugar. It has been

reported that reactions following the use of protamine zinc insulin have responded less readily to treatment than reactions caused by insulin. While this has not been observed by patients regulated on the régime herein described, it is wise to caution users of this new product so that serious results may be avoided, as there are always variations in the response of different individuals to any treatment.

Reactions usually follow: 1, too large a dose of protamine zinc insulin; 2, cumulation of its effect; 3, a too rapid increase in dosage while adjustment is being made; 4, the omission of all or part of a previous meal; and, 5, unusual exercise which greatly increases effectiveness of all insulin in lowering blood sugar.

Symptoms of hypoglycemic reaction may sometimes not accompany even a very low blood sugar, but the occurrence of nervousness, weakness, sweating, drowsiness, headache, nausea, slight mental disturbances, tingling of the extremities, visual disturbances, or any other unusual sensation should warn the patient. If treatment is not promptly initiated unconsciousness and more serious results may follow.

Treatment of reaction following protamine zinc insulin consists in taking 5 to 10 gm. of glucose or other sugar such as orange juice, honey, or cane sugar dissolved in water. This should be followed by 5 gm. of slowly absorbing carbohydrate, such as 2 saltine crackers, which should be repeated at intervals of an hour until the succeeding regular meal. If the reaction is severe, 10 to 20 gm. of glucose should be given intravenously. When in doubt about the approach of a reaction it is better for the patient to take 5 gm. of sugar and note the effect rather than allow the condition to proceed unchecked.

Prevention of hypoglycemic reactions is possible by exercising care in the amount of protamine zinc insulin given and in the distribution of food. The patient should also be warned about omitting or reducing meals or taking excessive exercise without a small amount of carbohydrate taken before hand. When the blood sugar tends to be low in the early morning the juice of an orange, subtracted from the breakfast, may well be taken at the same time as the injection, thus preventing any reaction before the time of breakfast. We always insist that patients become fully awake in the morning before taking their dose for the day, as we have seen several reactions occur because the injection was taken when a slight hypoglycemia was already present.

Storage of Protamine Zinc Insulin. Protamine zinc insulin keeps well if properly cared for. Unopened packages should be stored in a refrigerator. Vials in use need not be kept cold, but should be protected from heat, extreme cold, or strong light. None should be used after the expiration date which is stamped on each package.

Insulin. Wherever rapid action is required, insulin is more useful than protamine zinc insulin. It should still be used in the treatment of acidosis and infection and in preparation for operation and labor.

It may also be given temporarily in small doses as an adjunct to protamine zinc insulin during temporary conditions such as slight infections which upset the balance of the patient for a time.

Restrictions of the Diabetic. We have found that our patients respond well if we explain that their condition entails only two definite restrictions in their daily lives, namely: 1, strict adherence to diet; and 2, the taking of one dose of protamine zinc insulin daily. Beyond this they may live a practically normal life.

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THE ONE-HOUR TWO-DOSE GLUCOSE TOLERANCE TEST IN THE DIAGNOSIS OF DIABETES MELLITUS.

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VARIOUS glucose tolerance tests have been used as aids in the diagnosis of diabetes mellitus. The multiplicity of these tests suggests that no ideal one has as yet been devised. Such a test would be specific, would occasion a minimum of discomfort to the patient, and would require a short period of time. The most important factor from the diagnostic standpoint is the specificity of the test. Recently the literature concerning the oral glucose tolerance tests has been excellently reviewed by Myers and McKean.⁶

In the following study, 3 glucose tolerance tests were compared: the 3-hour 1-dose test described by Janney and Isaacson³; the 6-hour 2-dose test of Traugott⁵; and the 1-hour 2-dose test presented by Exton and Rose.^{2,4}

Three-Hour One-Dose Test. In the 3-hour test, the one most commonly used in this country, the criterion of diabetes is a blood sugar level at the end of the third hour which is above the fasting level.

This test was performed on a group of 59 non-diabetic patients taken at random from the medical wards of the William J. Seymour Hospital. Of this group 24 (40.7%) gave non-diabetic curves and 35 (59.3%) gave curves which would be called diabetic according to the aforementioned criterion. These 35 were senile patients with a generalized arteriosclerosis. A typical blood sugar curve obtained in these arteriosclerotics follows: Fasting, 94 mg.; 1 hour, 208 mg.; 2 hours, 183 mg.; 3 hours, 139 mg.

Figure 1 represents curves obtained with this test in a non-diabetic, a diabetic and an arteriosclerotic patient. It is impossible to decide from the curve whether the arteriosclerotic patient is diabetic or non-diabetic.

Other evidences of the non-specificity of this test were brought out by Beeler, Bryan, Cathcart, and Fitz,¹ who found a diminished tolerance in nephritis, arteriosclerosis, rickets, cancer, diseases of the liver, obesity, exophthalmic goiter, arthritis and pituitary disorders. Leyton⁵ also notices that "diabetic curves" may be obtained by this test in normal individuals.

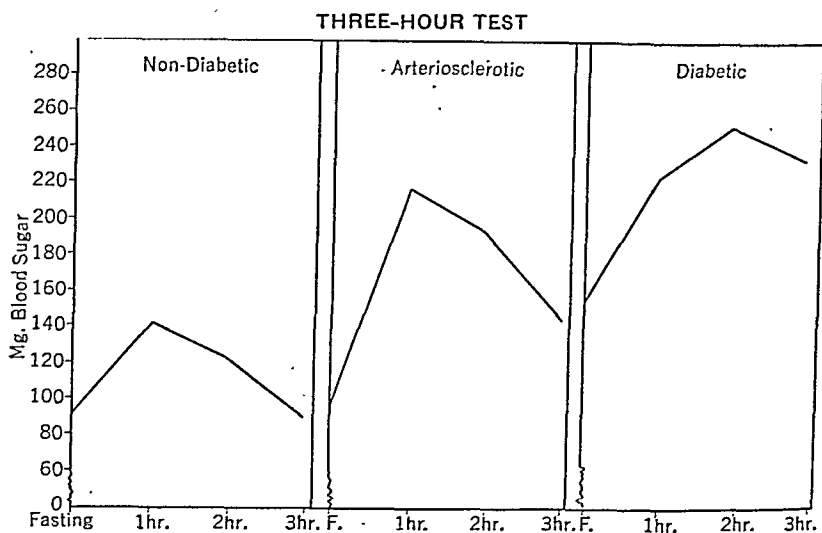


FIG. 1.—Typical 3-hour glucose tolerance tests. Note that the curve of the arteriosclerotic patient suggests diabetes.

Another disadvantage of this test was demonstrated by Sweeney,⁷ who showed that the curve obtained is influenced by the composition of the diet ingested during the 24 or 48 hours preceding the test. A high carbohydrate diet will increase the sugar tolerance; a high-protein diet will diminish the tolerance; and a high-fat diet will greatly decrease the glucose tolerance. Therefore, in order to determine the glucose tolerance accurately the test should be preceded by a regulated mixed diet for 2 or 3 days. It is obvious that the adoption of such a procedure is often quite impractical.

Six-Hour Two-Dose Test. The 6-hour test is based on the principle of Allen's Paradoxical Law, that the glucose tolerance limits in the diabetic are real while in the non-diabetic they are only apparent. In non-diabetics, the greater the amount of sugar given, the more is utilized; this is not the case in the diabetic.

In this test, blood for sugar determination is drawn in the fasting state and at hourly intervals for 6 succeeding hours. Immediately

after the fasting blood specimen and again after the third-hour blood specimen is obtained, a dose of 1.75 gm. of glucose per kilogram of body weight is ingested by the patient. In the diabetic the second dose of glucose will produce a second peak in the glucose level, and at the end of the sixth hour the blood sugar value will still be above the original fasting level. In the non-diabetic, the second dose of glucose may produce a slight rise, no rise or even a progressive decline in the glucose level, and at the end of the sixth hour the blood sugar value will be below the fasting level.

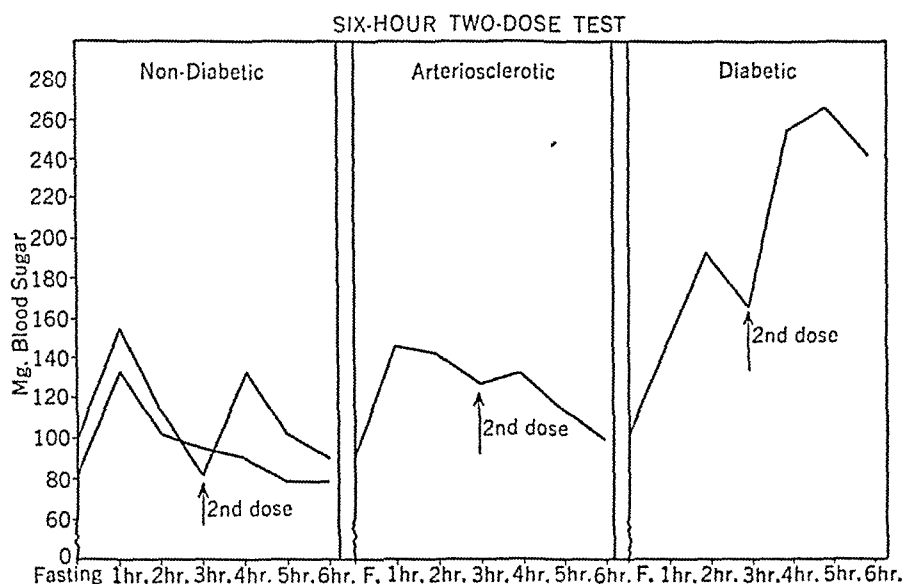


FIG. 2.—Typical 6-hour 2-dose glucose tolerance tests. Note that the second dose in the arteriosclerotic patient is followed by a curve that rules out diabetes.

The 6-hour test was performed on 138 patients of whom 44 were known diabetics, 32 senile patients with arteriosclerosis, and 62 non-diabetic patients suffering from various diseases not associated with disturbances of carbohydrate metabolism. Figure 2 shows the typical curves obtained in this experiment. In the non-diabetics the 6-hour test showed normal curves. In the arteriosclerotics it is seen that at the end of the third hour, the curve resembles that found in the diabetic; however, after the second dose of glucose the peak is lower than the first peak and at the end of 6 hours the blood sugar level comes within 10 mg. of the fasting level. It becomes evident that the limit of tolerance in this group is only apparent and not real and that therefore these patients are not truly diabetic.

In the group of 44 diabetic patients, both the 3-hour and 6-hour tests showed the same results.

The 6-hour 2-dose test is specific but it has the disadvantages of requiring a great deal of laboratory work and of necessitating 7 venous punctures in addition to starving the patient for the greater part of a day.

One-Hour Two-Dose Test. The 1-hour 2-dose test is also based upon the principle of Allen's Paradoxical Law but it has the advantage of being shorter and of requiring fewer venous punctures and blood determinations. Exton and Rose also showed that the antecedent diet does not affect the blood sugar curves in this test. These investigators originally advised that the 100 gm. of glucose be dissolved in about 650 cc. of water flavored with lemon juice and that half of this solution be given after fasting specimens of blood and urine are obtained. At the end of 30 minutes, blood and urine samples are again taken and immediately thereafter the second half of the glucose solution is given. Thirty minutes later specimens of blood and urine are again collected.

According to Exton and Rose "The typical criteria of normal responses to the 1-hour 2-dose test are: (1) A fasting blood sugar within the normal limits of the particular blood sugar method employed; (2) A rise in blood sugar which does not exceed 75 mg. in the 30-minute sample; (3) The blood sugar in the 60-minute sample is less, the same, or does not exceed the 30-minute sample by more than 5 mg.; and (4) All urine samples are negative to the Benedict's test.

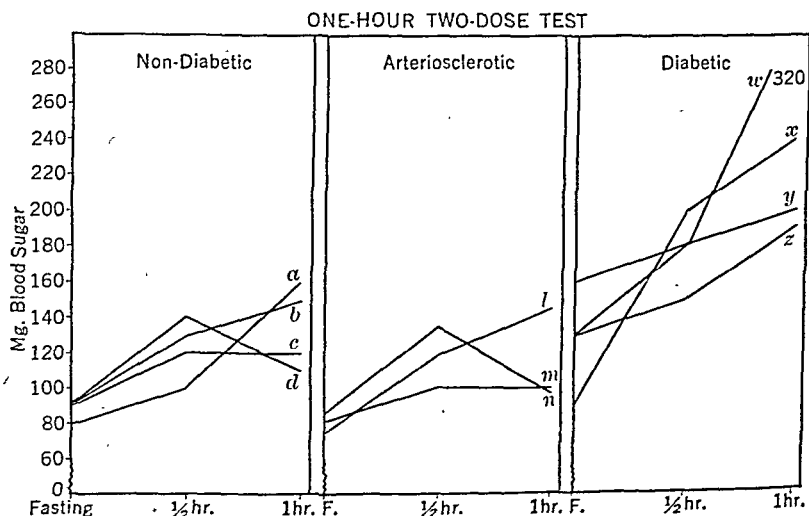


FIG. 3.—Typical 1-hour 2-dose glucose tolerance tests. Curves *a* and *b* of the non-diabetics and curve *n* of the arteriosclerotics fail to satisfy the criteria of Exton and Rose for the absence of diabetes.

"The criteria for determining diabetes in the 1-hour 2-dose test are a more or less steep rise of not less than 10 mg. of blood sugar in the 60-minute sample following the second dose of glucose and the relation of the blood and urine sugar values to the severity of the disease."

In the present study, the general principles of the test proposed

by Exton and Rose were retained, but the technique and interpretation were somewhat altered.

First, it seems logical that the weight of the patient should be taken into consideration in administering the glucose. Instead, therefore, of giving a standard amount to all patients regardless of size, the dosage of 1.75 gm. of glucose per kilo of body weight was retained. This calculated amount was then divided into 2 doses and given as described above.

Second, each gram of glucose was dissolved in 2.5 cc. of water, making a 40% instead of a 15% solution. This was done because the patients objected to the ingestion of the large volume of liquid necessitated by the weaker solution. Furthermore, similar results were obtained by the use of either concentration of glucose. In comparative tests done on 6 normal and 6 known diabetic patients, identical curves were obtained with the 40% and 15% solutions.

This modified 1-hour 2-dose test was performed on 240 patients, of whom 82 were known diabetics, 30 were senile arteriosclerotics and 128 were patients with diseases known not to be associated with disturbances of carbohydrate metabolism. Typical curves obtained with this test are shown in Figure 3.

In this graph the following 4 types of curves obtained in the non-diabetic are shown:

Curve.	Fasting, mg.	$\frac{1}{2}$ hour, mg.	1 hour, mg.
a	80	100	160
b	90	130	150
c	90	120	120
d	90	140	110

The following types of curves were found among the arteriosclerotics:

Curve.	Fasting, mg.	$\frac{1}{2}$ hour, mg.	1 hour, mg.
l	70	120	150
m	75	100	100
n	80	140	90

The group of known diabetic patients showed the following types of curves:

Curve.	Fasting, mg.	$\frac{1}{2}$ hour, mg.	1 hour, mg.
w	120	180	320
x	80	200	240
y	160	180	200
z	120	150	180

As is demonstrated in Figure 3, curves a and b of the non-diabetic and curve n of the arteriosclerotics fail to satisfy the criteria for the absence of diabetes. Because of such instances it seemed that the criteria of Exton and Rose should be modified.

These investigators claim that there is a clear-cut distinction between the form of the curve shown by the diabetic patient and

that shown by the non-diabetic patient in every single instance. Our findings, however, do not indicate this definite distinction in all cases. All of our diabetic patients satisfy the criteria of Exton and Rose for diabetes but so also do many of our non-diabetics. At 60 minutes, 59 of 158 (fully 37 %) of our non-diabetic patients (including arteriosclerotics) showed a blood sugar rise of at least 10 mg. above the 30-minute level. These patients would be considered by Exton and Rose to be diabetic.

An analysis of the figures obtained with this test in the three groups of patients showed that diabetes mellitus may be correctly diagnosed if at least 2 of the following 3 conditions are encountered: (1) A fasting blood sugar which exceeds 120 mg.%; (2) A half-hour blood sugar which exceeds the fasting level by 50 or more mg.; (3) A 1-hour blood sugar which exceeds the half hour level by 30 or more mg.

Our findings indicate that if a curve is obtained in which at least 2 of these 3 conditions do not exist, a diagnosis of diabetes mellitus is not justified. The equivocal curves were easily classified by applying this standard.

In order to test these standards, both the 6-hour and the 1-hour 2-dose tests were performed on 45 patients. The results are shown in the following table:

CLASSIFICATION OF PATIENTS BY VARIOUS TESTS.

No. of patients.	Six-hour test.	Criteria of Exton and Rose.	Author's criteria.
28	Diabetic	Diabetic	Diabetic
1	Diabetic	Diabetic	Non-diabetic
8	Non-diabetic	Non-diabetic	Non-diabetic
8	Non-diabetic	Diabetic	Non-diabetic

Taking the 6-hour 2-dose test as the standard of the presence or absence of diabetes, an analysis of these figures shows that the 1-hour test using Exton and Rose's criteria is 100% sensitive but only 50% specific. However, by applying the authors' criteria the test becomes 97% sensitive and 100% specific.

Conclusions. 1. The 3-hour 1-dose glucose tolerance test is not specific for the diagnosis of diabetes mellitus.

2. By using a 2-dose test, and thus applying Allen's Paradoxical Law, the true glucose tolerance can be determined and the diabetic differentiated from the non-diabetic patient.

3. While the 6-hour 2-dose test is specific in making this differentiation, it has the disadvantages of requiring a great deal of laboratory work and of causing a good deal of discomfort to the patient.

4. New criteria are proposed for the diagnosis of diabetes mellitus by the use of the 1-hour 2-dose glucose tolerance test.

The authors wish to express their appreciation to Miss Mary Winters and Miss Grace Kercher for their technical assistance.

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THE BLOOD KETONE CURVE AFTER A FAT TOLERANCE TEST.*

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Ketogenesis. Ketone bodies are a regular product of the intermediary metabolism of naturally occurring fatty acids by the process of beta oxidation. They are thus present in the blood normally, although in very small quantities. Hyperketonemia may result from an abnormal tendency to produce ketones or from an inability to oxidize them when they are formed. When for various reasons the breakdown of fatty acids is excessive, the ketone bodies accumulate in the blood; and, according to the prevailing theory, ketones are not further oxidized unless glucose is simultaneously burned. How this assistance to fat combustion is obtained is veiled in the obscurity that surrounds intermediate fat metabolism in general. The concept that "fat burns in the flame of carbohydrates" has led to much fruitful work on the subject of ketogenesis and anti-ketogenesis. The experimental evidence and the attempted formulation of a quantitative theory as to the rôle of carbohydrate in fat oxidation is adequately reviewed by Peters and Van Slyke.²³ They conclude that ketosis is due to the fact that ketones are not oxidized because of lack of carbohydrate in the metabolic mixture. This lack may be caused by insufficient exogenous supply of carbohydrate forming material, deficient endogenous stores, or impaired ability to oxidize carbohydrates.

That ketosis may also be the result of overproduction of ketone bodies is evident from studies on the physiology of the liver. This organ is the important site of ketone formation, as shown by perfusion experiments, by incubating fatty acids with liver slices (manometric technique of Warburg,¹⁶) and by studies after hepatectomy (Mann). The rapid disappearance of the hyperketonemia of depancreatized dogs⁸ after hepatectomy lends support to the theory of ketosis by overproduction. A definite parallelism exists here between the metabolism of fat and carbohydrates. This may be illus-

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trated in experimental pancreatectomy where a disturbance is set up in carbohydrate metabolism characterized by increased glyconeogenesis and underutilization of glucose; and by a disturbance in fat metabolism evidenced by increased lipemia due to augmented rate of mobilization of depot fat with accumulation of fat in the liver. Augmented breakdown of fatty acids ensues with the production of excessive ketone bodies and a rapid loss in body fat is noted. The administration of insulin restores the ability to metabolize fats in a normal manner and ketosis disappears. This fatty infiltration of the liver is associated with a multiplicity of clinical and experimental conditions; but the mechanism of its production is unknown, and the interference with liver function is not uniform. The subject is¹ably reviewed by Best^{5a,c} who has been able to prevent and cure accumulation of excess fat in the liver with choline. The entire problem is complicated by species difference in the ability to metabolize fats without ketosis, and by the possibility that fatty acids can undergo conversion to glucose, and glycogen may be an intermediate product in this process.¹⁹

Experimental and clinical observations are to be found in the recent literature which show that either directly or indirectly the pituitary gland influences metabolism of fat. The classical work of Houssay,¹⁴ amply confirmed, demonstrated that the cardinal symptoms of pancreatic diabetes including ketosis were considerably ameliorated when the hypophysis was removed. If small amounts of anterior pituitary extract are injected into the Houssay dog, symptoms develop including a return of ketosis. The more recent work of Long and his collaborators reviewed by Barr,⁴ tends to the conclusion that the action of the pituitary substance is possible only through the mediation of the adrenal cortex. That this is an anterior pituitary substance and is a special hormone, is the contention of Anselmino and Hoffmann,² whose work has been confirmed by some of those who have repeated it. Those isolating a ketogenic fraction from the anterior pituitary claim it is distinct from other pituitary factors and that the ketosis it produces is not associated with hyperglycemia. The present status of the ketogenic hormone, its specificity, nature, theory of action, etc., is well summarized by Collip.⁹ Anselmino and Hoffmann also state that the blood of patients in whom ketosis has been induced by a fat meal, when injected into test animals, causes a degree of ketosis similar to that which follows injection of their anterior pituitary factor, from which they conclude they have demonstrated this hormone in the circulating blood at the height of fat digestion.

Raab²⁴ concludes that it is the hormones of the posterior pituitary which play a rôle in fat metabolism. Blottner,⁷ after fat tolerance tests, concludes that insulin and extract of posterior pituitary have effects on fat metabolism that are of opposite nature. The clinical problems of fat metabolism have for long been correlated with gland-

ular and central nervous system lesions, especially in the diencephalon. It seems sufficiently established to take into account a hormonal regulatory factor controlling fat combustion and hence ketosis, and this gives additional support to the theory of overproduction of ketone bodies as the cause of ketosis.

The actual ketosis in diseased states must be due to various gradations and combinations of endocrinal and metabolic factors modified by local conditions in the organs where ketone formation and oxidation take place.^{13,25} Severe diseases of the liver, muscles or kidneys, *per se*, are rarely characterized by ketosis.

Ketonemia. No extensive studies of the ketone bodies in the blood are available. They have usually been estimated indirectly but neither the concentration of acetone in the urine nor determination of the alkaline reserve afford an accurate measure of ketonemia. Direct methods exist and depend on iodometric, colorimetric or gravimetric determination. This last, as in the method of Van Slyke, is the simplest and most specific when one wishes to measure the presence or extent of a definite ketosis. By this method under normal conditions, the ketone bodies seldom exceed 1 mg. %.²³ Hubbard¹⁵ by iodometric methods states the normal is from 0 to 3; Leites' co-workers²² report much higher figures. By the colorimetric method Goldzieher¹¹ finds 0 to 4. There is no agreement as to what the normal level is. Hyperketonemia is reported in alkalosis, pregnancy, starvation; according to Moore²⁰ in children, pyrexia, recurrent vomiting; and in glycogen disease, diabetes mellitus, etc. In a well controlled diabetic there is usually less than 5 mg. %; in coma these values rise to 300 and more mg. %.

Fat Tolerance Tests.—Although fat tolerance tests have been tried experimentally in many conditions, there is no agreement in the literature on the blood fat values in alimentary lipemia. A blood fat curve at best can only express a relationship between variations in absorption, mobilization or utilization, and storage. Wechsler,²⁷ in a search for the normal curve, obtained three patterns. The ascending type with a slow, non-progressive rise in total fats with slow return to fasting levels; the flat curve, although not a straight line, showed little variation from the fasting level; the descending curve with a progressive or steep decline and subsequent rise to the base line. No explanation is offered for the decrease in blood fat but other experiments in confirmation are cited. Sullivan and Fershtand²⁶ in determining fat absorption by the volumetric lipokrit method were able to obtain curves of a definite pattern in normal persons with a maximum rise of 65% in 6 hours, and a return to the fasting state in 9 hours. In diabetes, however, the curve was as in the normal except that 9 hours postprandially the level was still elevated to +42%. In diseases of the liver the absorption was diminished, at 6 hours +17%; and delayed, at 9 hours, +22%. The capacity of the organism to remove fats from the blood stream

is increased by feeding fats.²¹ This may be due to the fact that the fat metabolism hormone appears in the blood after the ingestion of fat. It has been noted that the second feeding of fat after hyperlipemia was established caused no further rise in the blood-fat level. No one has been able to obtain consistent fat-tolerance curves in animals partly because of the variation in the rate of fat absorption.

In general, very little is known about alimentary ketonemia. It was noted that the greatest lipemia goes hand in hand with the greatest ketosis.⁶ Leites¹⁷ states there is an adequate autoregulation of fat metabolism. When neutral fats and ketones are low, fat feeding leads to an increase, and when they are high, to a decrease, and that if lipemia and ketonemia are raised by fat feeding, a second test meal lowers the level. Goldzieher, Sherman and Alperstein¹¹ report that in their series of cases there is a physiologic rise in blood ketones after a fat meal, which they consider is due to stimulation of ketogenic hormone, but half their cases did not show it and that these were cases of pituitary deficiency. In most of these there was a drop in the level which they consider due to absence of ketogenic hormone. The following investigations were made to study ketonemia before and after a fat-tolerance test.

Methods. Blood ketone determinations were made on a series of patients after routine overnight fasts by the gravimetric method of Van Slyke.²³ Most of the patients were given a fat-tolerance test consisting of 75 gm. of butter on 15 gm. of gluten bread. This bread is very light and 15 gm. provides considerable surface. The meal was usually consumed within 15 minutes and the patients ate nothing further until conclusion of the test. Samples of blood were taken after 2, 3 and 5 hours and analyzed in the same way as the fasting sample. In some cases the blood glucose was simultaneously determined by the method of Folin and Wu.

These patients were all carefully investigated in the wards or out-patient department and the usual clinical and laboratory findings established the diagnoses.

Total ketones were determined and are expressed in mg. % as acetone. Readings of zero mean less than 1 mg. % as this is the limit of sensitivity and accuracy with this method.

Results and Comment. The control series (Table 1), show no ketonemia exceeding 1 mg. % in the fasting state in contradistinction to the cases of glycogen disease and diabetes mellitus. After the fat meal, the blood-ketone level remains flat and no hyperketonemia exists. In persons, then, who have no disturbance in carbohydrate or fat metabolism, the fat tolerance test provokes no physiologic rise in ketonemia above the threshold of 1 mg. %. Three cases of muscular disease were included in the series and 5 cases of liver cirrhosis because of the part these diseased organs might play in ketosis. These results are not in accord with the figures of Leites,²² who used a similar test but an iodometric determination. His figures, even when reduced to terms of ketones as

acetone, are much higher than any usually quoted. Goldzieher¹¹ does not give actual figures for all his cases.

TABLE 1.—BLOOD KETONE CURVE AFTER FAT-TOLERANCE TEST.

No.	Sex.	Diagnosis.	Total ketones as acetone in mg. %.					Comment.
			Fasting.	2 hrs.	3	5	9	
1	M	Muscular atrophy	0		0	0	0	1 week later.
2	M	Myasthenia gravis	0	0	0	0	0	
3	F	Myasthenia gravis	0	0	0	0	0	
4	M	Colitis	0		0	0	0	
5	F	Colitis	0	0	0	0	0	125 gm. butter.
6	F	Cholecystitis and obesity	0	0	0	0	0	
7	F	Cholecystitis and obesity	0	0	0	0	0	
8	M	Tuberculosis	0	0	0	0	0	
9	F	Tuberculosis	0	0	0	0	0	B. M. R. +58.
10	F	Cardiac	0	0	0	0	0	
11	F	Cardiac	0	0	0	0	0	
12	F	Cardiac	0	0	0	0	0	
13	F	Rheumatic fever	0	0	0	0	0	15 yrs. 105 kg. Child.
14	F	Leukemia	0	0	0	0	0	
15	F	Dermatitis and obesity	0	0	0	0	0	
16	F	Simple obesity	0	0	0	0	0	
17	F	Normal	0	0	0	0	0	Lues.
18	F	Normal	0	0	0	0	0	
19	F	Normal	0	0	0	0	0	
20	M	Normal	0	0	0	0	0	
21	F	Cirrhosis	0	0	0	0	0	Lues.
22	M	Cirrhosis	0	0	0	0	0	
23	M	Cirrhosis	0	0	0	0	0	
24	M	Cirrhosis	0	0	0	0	0	
25	M	Cirrhosis	0	0	0	0	0	Previously reported. ¹⁰
26	M	Nephritis	0	0	0	0	0	
27	F	Arthritis and obesity	0	0	0	0	0	
28	F	Gastric ulcer	0	0	0	0	0	
29	F	Diabetes mellitus	5.5		0	0	0	Controlled with insulin.
30	F	Diabetes mellitus	9.6					
31	F	Diabetes mellitus	84.7					
32	F	Diabetes mellitus	102.5					
33	M	Diabetes mellitus	156.6					Coma.
34	F	Glycogen disease	20.4					

Table 2 includes all cases of myxedema examined and each was found to develop hyperketonemia after the fat meal. Myxedematous patients usually have hyperlipemia in the fasting state and as the results show, no hyperketonemia. Since there is no evidence that the ability of the myxedematous organism to burn ketones is impaired, there must be then an abnormal tendency to produce ketones. This may be the result of augmented oxidation of fatty acids, which, if it is under hormonal regulation, means the organism responds to a fat meal with an overproduction of ketogenic hormone. That the pituitary is hypertrophic in some cases is well known; that this may occur experimentally after thyroidectomy is established.¹⁸ Further inferential evidence can be derived from Aron's³ observation of overproduction of thyrotropic hormone in myxedema. There is also the fact that, lacking thyroid hormone, these patients lack one of the inhibitory factors controlling pituitary secretions. The overproduction of ketogenic hormone is evident whether treatment was instituted or not. Thyroid therapy does not cure myxedema but alleviates some of the symptoms, in therapeutic doses it is not sufficient to inhibit the hyperhormonemia.

TABLE 2.—BLOOD KETONE CURVE IN MYXEDEMATOUS FEMALES.

No.	First B. M. R.	Chole- sterol, mg. %.	Ketones mg. %.				Present, B. M. R.	Cholesterol, mg. %.
			Fasting.	2 hrs.	3	5		
35	-14	364	0	11.9	2.0	4.4	Untreated	
36	-30	...	0	16.3	3.9	3.3	..	160
37	-22	...	0	3.9	2.3	5.0	Untreated	
38	-18	476	0	1.6	2.4	5.7	+10	106
39	-29	266	0	3.9	1.4	4.7	Untreated	} sisters
40	-40	...	0	0	3.8	3.2	= 0	
41	-12	320	0	3.3	3.3	3.7	+8	150
42	-19	...	0	1.3	1.9	6.2	-2	
43	-15	200	0	5.2	5.0	6.8	Untreated	

Other conditions in which disturbed production of pituitary hormones might be expected on clinical grounds were then studied.

TABLE 3.—BLOOD KETONE CURVE IN OTHER ENDOCRINOPATHIES.

No.	Sex.	Diagnosis.	Ketones in mg. %.				Comments.
			Fasting.	2 hrs.	3	5	
44	M	Acromegaly	0	0	0	0	Post Roentgen ray therapy.
45	F	Simmonds'	0	0	0	0	
46	F	Chromophobe- adenoma	0	0	0	0	Postoperative.
47	F	Cushing's	0	0	0	0	Post Roentgen-ray therapy.
48	F	Cushing's	0	5.0	4.0	1.2	
49	F	Cushing's	0	7.5	0	0	
			0	9.5	0	0	Repeated 2 days later.
			0	2.7	0	0	11 days menformone therapy
			0	5.7	0	0	7 days after therapy.
50	F	Pregnancy	1.7	8.9	13.8	25.2	
51	F	Pregnancy	8.6				Toxemia.
			2.3	1.6	3.4	7.6	3 weeks later.
			1.4	0	5.0	4.6	50 gm. glucose 1½ hrs. before test.
52	F	Pregnancy	2.3	5.3	4.9	6.5	
53	F	Pregnancy	1.2		1.8		No fat test.
54	F	Hirsutism	0	6.2	2.4	3.8	B. M. R. +13.
55	M	Cretin	0	0	0	0	Treated.
56	F	Cretin	0	0	0	0	Treated.
57	F	Cretin	0	0	0	0	Treated.
58	F	Cretin	0	0	0	0	Treated.
59	M	Cretin	0	1.2	3.2	2.5	Untreated.

The acromegalic in Table 3 and the first case of Cushing's disease were treated previously with irradiation to the hypophysis and gave normal curves. The second exhibited transient but considerable hyperketonemia on two occasions, which was reduced after menformone therapy which restored the normal menses to the patient who had been without them. After the therapy was discontinued, the ketosis after the fat meal was again more severe. The third case gave a hyperketonemic curve resembling the cases of myxedema, as did the patient with hirsutism. Simmonds' disease was negative, as was the chromophobe adenoma.

During pregnancy the concentration of ketone bodies in the blood rises. A pregnancy test based on this observation was advocated by Adlersberg and Porges.¹ It is also possible to provoke ketosis more rapidly and easily by carbohydrate starvation during pregnancy. Even without starvation, vomiting, or toxemia, ketosis is sometimes present. Pregnancy is also characterized by hyper-

hormonemia and modern pregnancy tests are based on this. In the gravida examined, there was ketonemia in the fasting state but very little more than normally. As the glycogen supply of the liver is easily exhausted and hyperlipemia exists, indicating mobilization of fat, this ketonemia is to be expected. After a fat meal the ketosis rises progressively to very high values. Fat combustion already augmented is greatly intensified by the overproduction of ketogenic hormone in response to the fat meal. Administration of glucose did not materially affect the ketonemia.

The four cretins, all treated with thyroid from an early age, did not show a hyperketonemic curve as did patients with myxedema; the fifth, untreated, did. It cannot be stated from this test whether the cretinism involves dysfunction of the fat metabolism hormone of the pituitary, or whether normal function was restored by therapy which in some cases was inadequate. It must be emphasized here that an underproduction or lack of ketogenic hormone will lead to no ketosis and hence the curve will be indistinguishable from that of normal controls. This may be the explanation for the flat curves obtained in several cases of hyperthyroidism, Cases 60 to 65 inclusive. If, however, the fasting ketonemia was elevated (Cases 66 to 69 inclusive) the response to the fat feeding was a drop in ketonemic level in the absorptive period with the return in the postabsorptive stage to the fasting level.

TABLE 4.—BLOOD KETONE CURVE IN ENDOCRINOPATHIES WITH FASTING HYPERKETONEMIA.

No.	Sex.	Diagnosis.	Ketones in mg. %.				Comments.
			Fasting.	2 hrs.	3	5	
60	F	Non-toxic goiter	0	0	0	0	Normal B. M. R. Menstruating.
61	F	Hyperthyroid	0	0	0	0	Di-iodotyrosine therapy 10 days.
62	F	Hyperthyroid	0	0	0	0	B. M. R. +63.
63	F	Hyperthyroid	0	0	0	0	B. M. R. +56.
64	F	Exophthalmic goiter	0	0	0	0	B. M. R. +39.
			0	0	0	0	B. M. R. +16; 4 weeks post-thyroidectomy.
65	F	Exophthalmic goiter	0	0	0	0	B. M. R. +62.
66	F	Exophthalmic goiter	5.2	0	0	6.2	Sugar tolerance abnormal. No fat given; B. M. R. +61.
			2.7	1.4	2.9	3.3	
67	F	Exophthalmic goiter	2.9	0	0	2.2	B. M. R. +59; menstruating. B. M. R. +4; 3 weeks post-thyroidectomy.
			0	0	0	0	
68	F	Exophthalmic goiter	4.9	0	0	6.2	B. M. R. +31; sugar tolerance abnormal. B. M. R. +8; 3 weeks post-thyroidectomy.
			0	0	0	0	
69	F	Exophthalmic goiter	5.0	0	0	4.9	B. M. R. +59. B. M. R. +6; 2 weeks post-thyroidectomy.
			0	0	0	0	
70	M	Fröhlich	9.4	0	0	4.3	B. M. R. -15; cholesterol 274 Pituitary type.
71	F	Lorain-Levi	6.6	0	0	3.9	
72	F	Obesity	6.8	0	0	2.4	
73	F	Obesity	3.8	0	0	2.9	
74	F	Endocrinopathy	7.0	0	0	3.9	
75	F	Endocrinopathy	5.0	0	0	4.9	}Twins.
76	F	Normal	0	0	0	0	

That there should be a fasting hyperketonemia in hyperthyroidism at times can be explained more readily than why fat feeding should abolish it. It is not apparently a function of the height of the metabolism. It may be an expression of liver damage. In hyperthyroidism a pseudodiabetic state may exist, but there is no impairment of glucose oxidation. There is a tendency to glycogen formation and to depletion of liver glycogen stores, and to hyperglycemia in early stages with insulin sensitivity. There is concomitantly a greater metabolism of fat with hyperlipemic stages and storage in the liver, mobilization of depot fat and loss in weight. Hypolipemic stages are also noted. Hepler¹² reviewed the controversial evidence of fat tolerance in hyperthyroidism and reported experiments to show that lipemia varied with the stage of hyperthyroidism. Whether the fat is streaming to the liver for transformation to carbohydrate is still an unsettled question. There is at least in some cases, augmented oxidation giving rise to ketones because ketosis has been observed by many in Graves' disease. In these cases ketosis was abolished by the fat meal because, perhaps, there is no ketogenic secretion precluding the oxidation of the fat which was fed, the absorption of which temporarily prevents the augmented oxidation of endogenous fat. Those cases examined after thyroidectomy all showed a normal curve.

Other endocrine cases (70 to 75 inclusive), with a definite fasting hyperketonemia also showed a drop after the fat meal. That these must also be attributed to a combination of disturbed intermediate metabolism and absence of tropic hormone secretion is probable. Patients 75 and 76 were twin girls, 11 years of age, blondes, who formerly looked alike. In recent months one began to develop an endocrinal disturbance demonstrated by headache, well developed mammæ, pubic hair, and a thickness of the face and body associated with mental retardation, and was quite unlike the twin sister who is mentally alert and shows no signs of puberty. The basal metabolism and cholesterol of both were quite similar and within normal limits. The sella turcica was normal in each, the fundi were normal. The child with endocrinopathy had a slight but measurable exophthalmos. The normal one of the twins has a negative ketone curve but the other shows definitely a fasting ketosis.

Because of the work of Best^{5b} on fatty infiltration of the liver and its prevention and cure with choline, the following patients are included, who gave typical hyperketonemic curves, and in whom the hyperketonemia might well be due to fatty livers. The last 2 cases were treated with choline. While on their regular diet the day after the first test they received 1 gm. of choline each, which dose was repeated on the second day, and the third day 2 hours before the fat tolerance test was repeated, they each received 200 mg. The results of the test after choline administration show that fasting ketosis was abolished and a marked drop in the ketonemic level

after fat feeding took place. This is definitely against the theory that the action of choline is to accelerate the metabolism of fat in the liver.

TABLE 5.—BLOOD KETONE CURVES AFTER CHOLINE THERAPY.

No.	Sex.	Diagnosis.	Ketones in mg. %.				Comments.
			Fasting.	2 hrs.	3 hrs.	5 hrs.	
77	F	Hepato-splenomegaly	5.0	3.7	4.3	1.2	
78	F	Hepatomegaly, colitis	0	0	2.6	2.7	
79	F	Cyclic acetoneuric vomiting	5.5	12.6	10.1	4.9	
80	F	Chronic glomerulonephritis	0	5.4	0	1.2	After choline.
			0	8.6	4.7	1.8	
			0	3.7	1.2	0	After choline

The last table shows that before and after the fat tolerance test there is no variation of the blood glucose level beyond normal limits. In no case was hyperglycemia or hypoglycemia noted. The general tendency in those patients developing hyperketonemia after fat feeding, was towards a lower glycemic level.

TABLE 6.—DETERMINATION OF BLOOD SUGAR IN MG. % SIMULTANEOUSLY WITH KETONES BEFORE AND AFTER FAT TOLERANCE TEST.

No.	Diagnosis.	Fasting.	2 hrs.	3 hrs.	5 hrs.
36	Myxedema	88	76	80	84
37	Myxedema	100	98	86	104
38	Myxedema	82	78	92	96
40	Myxedema	80	70	74	80
35	Myxedema	80	80	86	80
10	Cardiac	92	100	100	88
22	Cirrhosis	88	86	78	86
15	Dermatitis	94	96	88	90
49	Cushing's	94	...	78	88
58	Cretin	84	82		
66	Graves'	80	88	86	80
71	Endocrinopathy	96			
50	Pregnancy	80	84	84	76
9	Tuberculosis	84	78	90	80
12	Cardiac	76	78	78	82
45	Endocrinopathy	80	78

Conclusions. Normally no significant ketonemia exists and after a fat tolerance test hyperketonemia does not develop. If the fat meal provokes increased secretion of ketogenic hormone, fat combustion is augmented and hyperketonemia develops. Such a test meal will not differentiate stimulation of normal quantities of ketogenic hormone from lack of it as neither condition results in ketosis.

Hyperketonemia in the fasting state is indicative of augmented endogenous fat metabolism associated disturbance of carbohydrate metabolism, or inability to oxidize ketones formed in the course of intermediate fat oxidation. When hyperketonemia exists a fat tolerance test will result in increased ketosis, decreased ketosis, or constant ketosis depending on the increased, decreased, or normal secretion of ketogenic hormone respectively, but the state of fatty infiltration of the liver can modify the results independently of the endocrine balance.

Myxedema is a condition in which a fat meal calls forth excessive ketogenic hormone and hyperthyroidism is the reverse. Conditions clinically attributed to hyperfunction of the pituitary react like the former with ketosis, those due to underfunction give rise to no ketosis after the test, as in the latter.

Summary. A fat tolerance test is described with the level of the blood ketones as the indicator. This is a useful procedure in elucidating disturbances in fat metabolism and its endocrinal regulation.

The blood ketone curve after this fat tolerance test is described and its interpretation is discussed in a series of control cases and a series of endocrinopathies.

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THE TOXICITY AND EFFECT OF CONGO RED UPON BLOOD COAGULATION.

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CONGO red has been employed, among other clinical tests, for the estimation of the functional state of the reticulo-endothelial system and as a test for amyloid disease.^{4,12} It has also been used empirically in treating pernicious anemia.⁸ The dye is reported

to be advantageous as a hemostatic agent in cases of pulmonary tuberculosis,^{1,6} uterine bleeding,^{5,11} teeth extraction in hemophiliacs⁶ and purpura hemorrhagica.¹³

In studying the effect of Congo red on coagulation time, Becker¹ injected 5 patients who were bleeding (4 from the lungs) with Congo red and obtained almost immediate arrest of the bleeding. Coagulation time determined 24 hours after injection was found to be diminished. The most significant changes which Becker obtained, however, were in those cases where the coagulation time was abnormally long before injection. When the same patients were tested 3 days later, the coagulation time was normal and further injection of the dye reduced the time only slightly, if at all. This finding raises the question, Does Congo red shorten coagulation time which is already within the normal range?

Behr,² using the coagulation time method of Heubner and Ronna, reports an increased coagulation (decreased coagulation time) in patients having non-infectious disease, following the injection of the dye. Likewise, Wedekind^{14b} reports increased coagulation (Burker's method) in normal patients and those without infectious disease. Belonoschkin and Wöhlisch,³ using normal students as subjects, claim to have demonstrated an increased fibrinogen content of the blood 24 hours after the injection of Congo red. The injection of the dye is also said to be followed by monocytosis,^{6,9,13,14b} increased platelets^{1,2,6,9,13,14b} and by an increase in sedimentation rate.² The clinical dose ordinarily used is 10 cc. of a 1% solution, given intravenously.

Since Congo red in solution is a colloid, it is to be expected that when injected the dye will be taken up by the phagocytes of the reticulo-endothelial system. This has been shown to be the case of Wedekind^{14a} with injections of other colloidal solutions, such as trypan blue and carbon dust. After producing sterile inflammation, trypan blue was injected intravenously and later found concentrated in the phagocytes which had collected around the inflamed area. Because the cells of the reticulo-endothelial system ingest the dye particles, it is thought by some authors, particularly Díaz,⁶ that the action of Congo red is mediated through a stimulation of this system. At the present time, however, there seems to be no adequate explanation of the exact mechanism by which stimulation of the reticulo-endothelial system could increase coagulation.

Nikolajew and Gurewitsch,⁹ finding that Congo red shortens coagulation time, suggest that the endothelial cells of the capillary walls ingest the dye particles, become engorged and thus cause partial constriction of the capillaries. It is this constriction of the capillaries which makes coagulation more rapid. This explanation seems possible in regard to diminished bleeding time, but we cannot believe it adequate to explain diminished coagulation time.

Since Congo red has apparently been used with some success as

a clinical hemostatic agent, it seemed wise to investigate further its effects when injected intravenously into laboratory animals. In addition, its effects upon blood coagulation were studied upon a small series of patients. Congo red has not only been used as a coagulant, but is known to be an anticoagulant as well, although in the latter capacity it appears to be less effective and more toxic than other dyes of the diazo direct type.⁷ Because of these antithetic actions of the dye it seemed important also to investigate the effect of various doses.

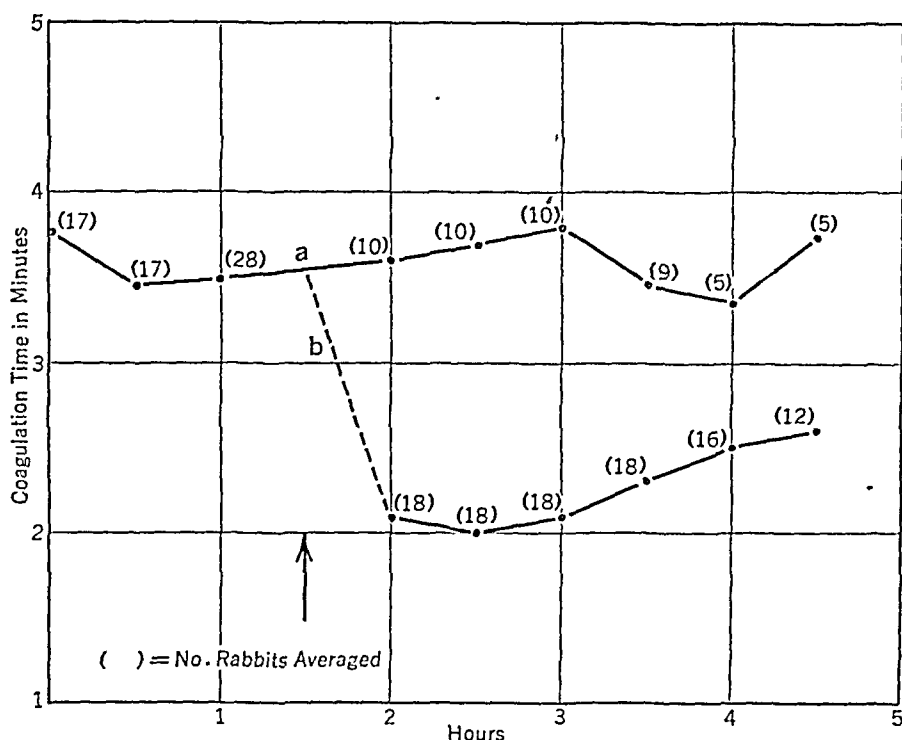
Methods and Subjects. In the present experiments coagulation time was determined on rabbits, dogs and human subjects before and after the intravenous injection of Congo red. The method used was a modification of the capillary glass tube method. The capillaries were 0.5 to 1 mm. in diameter and 10 cm. long. The tubes were individually standardized by placing them in a dish containing 15 cc. of 70% alcohol. Only those tubes were used in which the alcohol rose to a height of 6 to 8 cm. By this standardization variations in the size of the capillaries were reduced to a minimum. The tubes were dried in an oven and kept covered until used.

Rabbits. *Congo Red as a Coagulant.* Four breeds of young adult rabbits were used: rufus red, chinchilla, Belgian and albino. Differences in breed appeared to have no influence upon the effect of the dye. The rabbits were kept on a diet of hay and oats for some weeks previous to the experiment.

The ear of the rabbit was shaved clean in the region of the marginal vein, the vein was slit with the point of a sharp scalpel blade and the blood allowed to flow until 4 or 5 drops had escaped and had been wiped away. By allowing the ear to bleed freely in this way, we believe that contamination by tissue fluid was negligible. Blood from the next drop was allowed to flow into one of the capillary tubes. Fragments were broken off at $\frac{1}{2}$ -minute intervals. Coagulation was judged as the point at which a thread of fibrin spanned the gap between two pieces of the capillary. With practice, judgment of the end point became satisfactorily accurate and consistent. Duplicate and sometimes triplicate tests were made for each determination.

After several control tests had been made on each of 2 or 3 rabbits, 1 to 5 cc. of physiologic salt solution were injected into the marginal vein of 1, and the same volume of 1% Congo red (10 to 20 mg. per kg. body weight, in physiologic salt solution) was injected similarly into the others. The subsequent coagulation time tests were made from the ear opposite to the one injected. The individual curves of 18 rabbits injected with Congo red and 10 rabbits injected with physiologic salt solution have been averaged and are shown in Graph I. As is readily seen, the coagulation time of rabbits injected with normal saline remains practically unchanged, while coagulation time following Congo red is decidedly diminished

within an hour, and continues at a low level for at least 3 hours after injection of the dye. Nikolojew and Gurewitsch⁹ mention experiments in which they found diminished coagulation time in rabbits 24 hours after injection of Congo red.



GRAPH I.—Blood coagulation time in rabbits. Arrow indicates intravenous injection of (a) physiologic salt solution, and (b) Congo red.

Bleeding Time. The injection of small doses of the dye (1 to 5 cc.) intravenously in rabbits caused not only a shortened coagulation time, but also a marked diminution in bleeding time. This was usually apparent within a few minutes after injection. When a fresh cut was made for the next coagulation test, the wound bled only slightly. It was often necessary to heat the ear in order to obtain sufficient bleeding to allow the passage of 4 to 5 drops. If necessary, the ear was held near the bulb of a desk lamp until the vessels were engorged. When bleeding commenced, the lamp was immediately removed, and the blood allowed to flow freely. Thermostimulation seemed less likely to influence the test than the mechanical stimulation of rubbing the ear.¹⁰ Control experiments on uninjected rabbits showed that stimulation with heat and immediate removal of the source of heat as described did not influence coagulation time.

Since small doses of Congo red cause a decreased bleeding time and a decreased coagulation time in the rabbit, it would be expected that large doses which produce prolongation of coagulation time

would likewise lengthen bleeding time. This was readily observed in the animals used to determine toxicity. If the ear vein was cut after a massive dose had been administered, persistent hemorrhage occurred almost invariably.

Congo Red as an Anticoagulant. As already stated, the dose of Congo red used in these experiments to shorten coagulation time was 1 to 5 cc. (10 to 20 mg. per kg.) of a 1% solution. When massive doses of the dye were used the opposite effect was obtained, coagulation time being greatly prolonged within a short time after injection. In 5 rabbits injected intravenously with 200 to 500 mg. of Congo red per kg. of body weight, the blood showed an extraordinary prolongation of coagulation time, the values ranging from 15 minutes to no coagulation after 5 hours.

Toxicity. The toxicity of Congo red for rabbits has been determined by intravenous injection of massive doses of the dye. As shown in Table 1, the minimal lethal dose (M.L.D.) is about 300 mg. per kg. of body weight. After the administration of fatal amounts death occurred within 24 hours. The animals showed no characteristic symptoms prior to death.

TABLE 1.—INTRAVENOUS TOXICITY OF CONGO RED FOR RABBITS.

Dose, mg/kg.	Number of rabbits injected.	Number died.
200	7	2
300	6	5
300-500	4	4

Effect of Congo Red in Vitro. The effect of Congo red in 1%, 0.5%, 0.1%, 0.01% and 0.001% solutions was studied *in vitro*. Two test tubes 5 cm. long, having an inside diameter of 1.1 cm., were used in each case. One of these contained 0.2 cc. of the Congo red solution to be tested while the other contained the same volume of physiologic salt solution, the latter being the control tube. Two cc. of blood were withdrawn from a rabbit's heart into an oiled syringe for each test. One cc. of blood was immediately put into the test tube containing the Congo red solution, while the other was added to the salt solution. The end of the needle was kept in the solution while introducing the blood so that thorough mixing of the blood and the test solution was assured. The end point for coagulation was taken as the time at which the tubes could be inverted without allowing the blood to run down the side (Howell method).

The results (Table 2) showed that the dye when added in a concentration of 1% and 0.5% solution, lengthened coagulation time *in vitro* so that clotting did not occur even after many hours. Congo red in 0.1% solution increased the time to some extent, and in dilution of 0.01% and 0.001%, the presence of Congo red did not affect the coagulation time. It appears that large amounts of Congo red

cause prolongation of coagulation time *in vivo* and *in vitro*, and that small amounts diminish coagulation time *in vivo* but have no effect *in vitro*. It is therefore assumed that physiologic reaction to the dye is necessary to effect a decrease in coagulation time.

TABLE 2.—THE EFFECT OF CONGO RED ON BLOOD COAGULATION TIME IN VITRO.

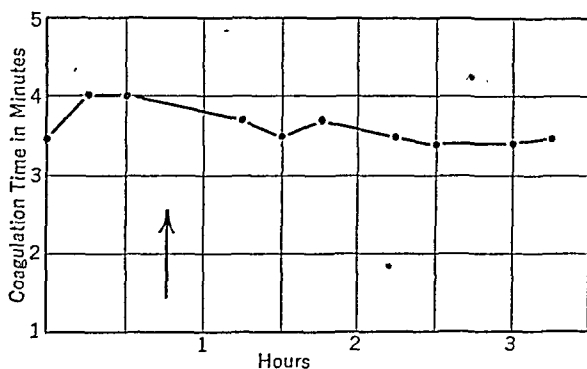
Rabbit (blood from).	Congo red solution.		Coagulation time (min.)		
	Per cent.	Mg. in 0.2 cc.	1 cc. blood with 0.2 cc. Congo red.	Final conc. dye, %.	1 cc. blood with 0.2 cc. saline.
I . . .	1.00	2.00	No coagulation	0.17	3.00
	1.00	2.00	No coagulation	...	2.75
	0.50	1.00	No coagulation	0.08	2.00
	0.50	1.00	No coagulation	...	3.00
II . . .	0.10	0.20	12.00	0.017	5.00
	0.10	0.20	8.00	...	6.00
	0.01	0.02	5.00	0.0017	6.00
III . . .	0.01	0.02	4.50	...	4.50
	0.001	0.002	5.00	0.00017	5.00
	0.001	0.002	6.50	...	6.50

Dogs. The investigation of coagulation time following intravenous injection of small doses of Congo red into dogs was made in the same way as described above. Two series of experiments were performed upon 4 dogs. As shown in Graph II, which gives the average values obtained, the results in this case were negative for the period of about 3 hours after injection. The doses ranged from 5 to 20 mg. per kg. This amount was comparable to that which the rabbits received (10 to 20 mg. per kg.). These negative results in the dog may be due to a difference in the time of response to the injection, or to an unequal tolerance of the dog for Congo red. On the other hand, the difference in the reaction of the two animals may be more fundamental, that is, an example of a specific variation.

Patients. Twenty convalescent patients on the medical wards were subjects for this study. Intravenous injections of 10 to 15 cc. of 1% Congo red were given. Coagulation time tests were made before and after injection. In the first 10 cases the blood was obtained from the finger tips. Even though the standardized capillary tubes were used, the results employing this technique showed such wide variations both in control determinations and after the administration of the dye that they were regarded as of little value for our study.

Since it was believed that the coagulation time in the latter cases was greatly influenced by the amount of tissue fluid withdrawn with the blood from the finger, venepuncture was performed to obtain the blood in the remaining 10 cases. With the needle in the vein the syringe was removed and the blood allowed to flow out steadily through the needle. After a few drops had escaped, one of the capillary tubes was filled with blood directly from the end of the needle. Two or three tubes were generally used, each filled from a different drop of blood. In practically all cases observations upon

the tubes of one test checked with each other as closely as can be expected with any subjective method. Coagulation time tests made in this way from venous blood are by far more accurate than those made on blood from the fingertips. Examination of Table 3 shows that coagulation time was diminished after the injection of Congo red in the majority of the subjects studied.



GRAPH II.—Blood coagulation time in dogs. Arrow indicates intravenous injection of Congo red.

TABLE 3.—BLOOD COAGULATION TIME (MINUTES) IN PATIENTS FOLLOWING INTRAVENOUS INJECTION OF 1% SOLUTION OF CONGO RED (10 CC.).

Case.	Previous day.			Injection at 11.05 A.M.			Day after.
	11 A.M.	11.30 A.M.	4.30 P.M.	11 A.M.	11.30 A.M.	4.30 P.M.	11 A.M.
1. Pulmonary tuberculosis	4.50 4.50 5.00	2.75 3.50	4.00 4.50	5.00 6.00
2. Pulmonary tuberculosis	9.00 8.50 9.00	9.00 9.50	4.00 3.50	8.50 9.50
3. Pulmonary tuberculosis	4.50 5.00	5.00 5.50	4.50 5.00	7.00 7.50	2.75 3.00	7.00 8.00	6.00 6.25
4. Bronchial pneumonia	4.25 4.75	4.50 4.75	3.50 3.75	3.50 4.00	4.50 4.50	3.00 3.50	3.50 4.00
5. Bronchial pneumonia	5.00 8.25 8.75	3.00 3.25 3.50	4.00 4.00 4.50	7.50 7.00 5.75
6. Laryngitis	6.00 6.50	5.00 6.00	5.00 5.00	6.00 6.00	4.50 4.25	3.00 3.50	5.75 6.00
7. Hemorrhoids*	9.00 7.50 9.00	6.75 7.00	7.75 ..	5.50 5.50
8. Multiple myeloma	9.00 9.25 4.25	5.25 5.75 5.00	6.00 5.50 6.00	8.50 8.50 7.00
9. Diabetes mellitus	4.25 5.00	4.50 4.50	5.50 6.00	5.00 6.00	6.00 6.00	6.50 5.50	6.00 6.00
10. Hysteria	6.00 6.50	6.00 6.50	6.00 4.50	6.00 6.50	3.50 3.50	5.50 6.00	6.00 5.50

* Received 15 cc.

Summary. Congo red injected intravenously in small doses, 1 to 5 cc. of 1% solution (10 to 20 mg. per kg. of body weight), diminishes the coagulation time in rabbits as determined by a modified capillary glass tube method. In large doses (200 or more mg. per kg.) the coagulation time is greatly increased. Bleeding time in rabbits is greatly decreased by the injection of the dye in small

amounts, and is conversely increased by the injection of large amounts. The M.L.D. of Congo red for the rabbit by intravenous injection is about 300 mg. per kg. With rabbit blood large amounts of Congo red cause a prolongation of coagulation time *in vitro* and after administration *in vivo*, while small amounts diminish coagulation time *in vivo* but have no effect *in vitro*.

Congo red in small doses (5 to 20 mg. per kg.) has no effect on the coagulation time of dogs over a period of about 3 hours subsequent to injection.

In 10 patients injected intravenously with 10 to 15 cc. of a 1% solution of Congo red, tests made on blood from the veins showed, in the majority of instances, a definite decrease in coagulation time following administration of the dye.

We wish to thank Dr. N. Bloom, of the Department of Medicine, for his very generous coöperation in facilitating the experiments herein reported upon patients in the medical wards.

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DIETARY DEFICIENCY AS A CAUSE OF MACROCYTIC ANEMIA.

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THE rôle of dietary deficiency in the production of an anemic state has been stressed repeatedly (Elders,¹³ Minot,²⁷ Aron,³ Cornell,¹⁰ Keefer and Yang,²⁰ Kern,²¹ Castle and Minot⁶). In accordance with the views of Castle, the nutritional anemias may be divided into the direct or primary types, in which a poor diet has been the main cause of the anemia and the so-called conditioned or secondary types, which are due to an inadequate utilization by the body of an otherwise complete diet. In many instances *both* a direct dietary deficiency and some abnormality of the body have led to the anemic state, for instance, in the anemias of chlorosis, chronic blood loss, pregnancy, the various forms of anemia associated with gastrointestinal diseases, hookworm disease, and so on.

Most of the recorded cases of *primary* deficiency anemia have been of the hypochromic, microcytic type which is caused particularly by a deficiency in iron. Macrocytic anemia is usually of the conditioned type, as exemplified by pernicious anemia, in which an intrinsic factor is lacking from the stomach, or in certain cases of sprue where diarrhea deprives the body of its supply of blood-building material. Cases of macrocytic anemia due primarily to a food deficiency (lack of Castle's *extrinsic* factor) have been described by Balfour and Wills³⁴ in British India, where they seem to be most common in pregnant women. The literature contains only a few case reports of a similar anemia in the temperate zone (O'Hara and Grewal²⁸, Kern,²¹ Longcope²³). In our opinion, macrocytic anemia due to lack of extrinsic factor is not so rare as the scarcity of case reports might lead one to believe.

Case Reports. CASE 1.—Mrs. W. M., aged 33, a married housewife, was admitted to the Department of Medicine of this university (Service of Professor Snapper) on August 3, 1931. Three years previously the patient emigrated with her husband to the woods of Venezuela, where she ate chiefly canned vegetables, canned milk, rice and bread. She did not eat any meat or eggs and only occasionally an orange or banana. The appetite became very poor. After 2 years she went to the Dutch East Indies, also away from any white settlement. She continued to take a poor diet consisting almost entirely of bread, rice, and canned vegetables; seldom did she eat potatoes and fresh milk, and very rarely eggs, meat, or chicken. A few months after her arrival in the Indies, she developed diarrhea which lasted for a few days and then constipation developed. Her appetite disappeared completely and vomiting commenced for no known reason, so that she mistakenly thought that she might be pregnant. Weight loss ensued and pallor, fatigue and palpitation developed. As no treatment seemed to be able to relieve the vomiting, she was advised to return to Holland.

Menstruation had always been regular and of normal quantity. Previous history and family history were irrelevant. Her son aged 11 was healthy. She never had any abortion or abnormal loss of blood through other causes.

On *physical examination*, immediately after her return to Amsterdam, the patient was in a deplorable condition. She was very thin (weighing only 40 kg.) and pale. The skin was dry and showed a brown patchy pigmentation over the face, abdomen, and dorsum of the hands. The tongue was smooth, the teeth absent. The lungs were normal. A systolic murmur was audible over the whole of the precordium. The abdomen showed no abnormalities, the spleen was barely palpable. Both fundi of the eyes showed small hemorrhages. The neurologic findings were normal. Blood pressure was 90/45; pulse 120; temperature varied between 37° and 38° C.

The urine contained a small trace of albumin and an excess of urobilin. There was no occult blood in the stools; the feces were well formed and on microscopic examination contained no parasites or poorly digested food particles. The Wassermann and Pirquet reactions were negative; the van den Bergh reaction normal.

The fasting stomach contained, 1 week after admission, no free hydrochloric acid. Two hours after a test meal of 400 cc. broth, the acidity values rose to 15 free and 62 combined hydrochloric acid (Fig. 1). The quantity of gastric juice obtained was small and contained much mucus and many leukocytes. Duodenal intubation revealed the presence of many leukocytes both in the duodenal juice and in the so-called "gall bladder bile." The diastase concentration was 640 Wohlgemuth units (normal value).

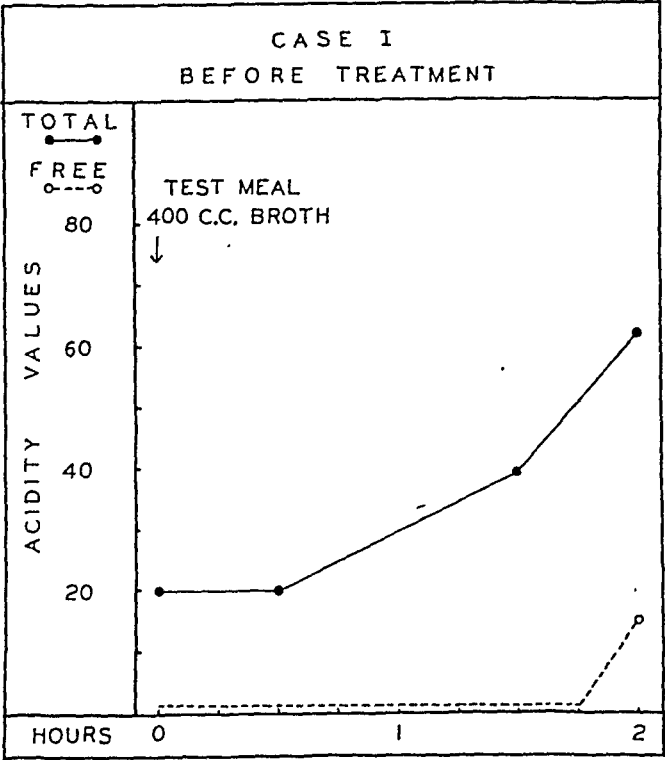


FIG. 1

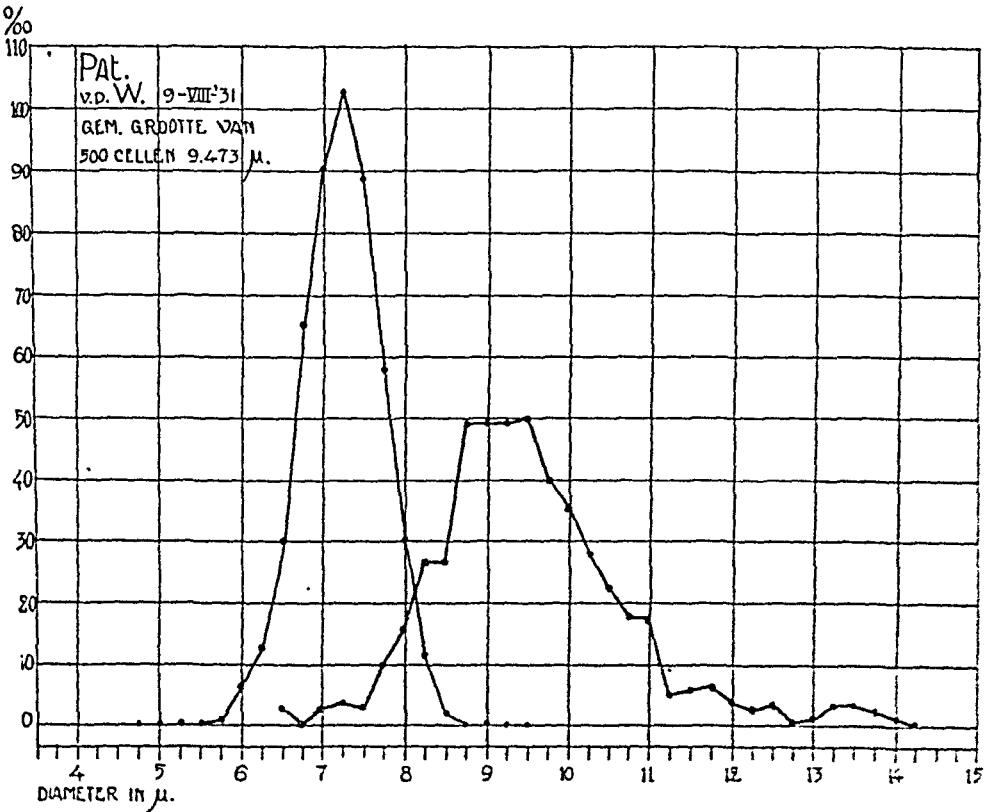


FIG. 2 —Case 1. Price-Jones curve.

A blood sugar tolerance curve after administration of 50 gm. of glucose by mouth, started from a fasting level of 74 mg. per 100 cc. and rose to only 106 mg. per 100 cc. after 1 hour.

The *blood picture* was as follows: hemoglobin 35% (Sahli), red blood cells 1,450,000 per c.mm., color index 1.3. White blood cells 2800 (stabs 3%, neutrophils 50%, eosinophils 1%, monocytes 9%, lymphocytes 37%). The red blood cells showed a marked anisocytosis, poikilocytosis, *megalocytosis*, and polychromasia. No nucleated red cells were seen. The Price-Jones curve is shown in Figure 2. The average cell diameter was 9.47 micron. The reticulocytes numbered 0.2%.

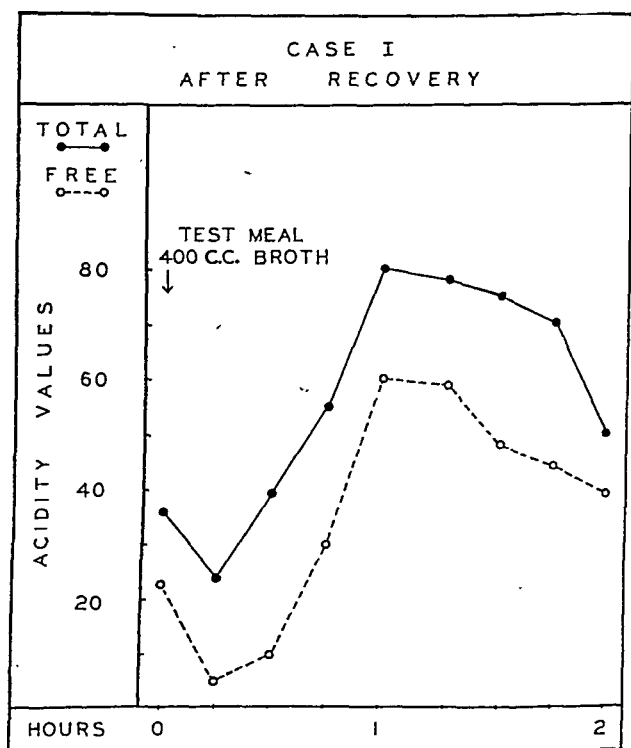


FIG. 3

The diagnosis at that time was pernicious anemia, in spite of the fact that there was some free hydrochloric acid in the stomach after the test meal. The patient received two blood transfusions, a mixed diet, diluted hydrochloric acid, iron, whole liver by mouth and liver extract intramuscularly. She made a rapid recovery, the vomiting ceased, and she gained 7 kg. in 7 weeks. Three weeks after admission, the hemoglobin had increased to 55%; on discharge, 7 weeks after admission, she had 100% hemoglobin and 4,500,000 erythrocytes. The pigmentation disappeared.

September 4, 1931, 4 weeks after admission, a new examination of the gastric contents showed free hydrochloric acid in the fasting stomach (acid values 23/36), and the acidity curve was of a "high" type: 1 hour after administration of the test meal the acid values were 60 free and 80 combined hydrochloric acid. The amount of gastric juice was notably greater than on the first examination (Fig. 3).

The patient was discharged September 24, 1931. Her condition since then has been excellent. *She stopped taking liver and liver extract immediately after her discharge from the hospital.* She has stayed in Holland ever since, and now takes a mixed diet containing plenty of meat, fruit and vegetables. A recent blood examination, 6 years after discontinuing the liver treatment, revealed no abnormalities.

CASE 2.—A girl, K. B., aged 14, was admitted to the Department of Medicine of this university February 5, 1935.

Birth and infancy had been normal; besides bronchitis and pneumonia at the ages of 5 and 9, respectively, there had been no previous illnesses of significance. At the age of 12, she was treated in another hospital for a poor appetite, weakness and anemia.* The next year she was sent to the country for similar complaints but 6 months later, or in the half year before we studied her, her weakness and pallor increased markedly. Indeed, during the whole of the last year she had been troubled with a sore mouth and tongue so that "acid" food could not be taken and the anorexia became greatly aggravated. She had become depressed and irritable. Four weeks before admission she developed "abdominal flu" with fever, headaches, two nosebleeds and diarrhea. After she recovered from this illness she remained tired and complained about dizziness. The bowels, however, soon became regular.

Half a year before admission menstruation commenced and occurred regularly every 4 weeks for 3 days; the amount of blood loss was normal. There was no loss of weight and no symptoms or signs referable to the respiratory, circulatory or genitourinary systems.

The dietary history revealed some interesting facts. It appeared that the family lived under extremely poor financial conditions. The total income for 5 people amounted to \$12.00 (18 guilders) a week, of which \$3.00 had to be paid for rent. The family had always been vegetarian. Two years ago after the patient's father died, it became increasingly difficult for them to maintain a varied vegetable diet on this low income. Finally, the family ate chiefly bread, oleomargarine and brown sugar, but 3 or 4 times a week they had vegetables and potatoes. After 1 year of this diet they all felt so weak that they gave up the vegetarian regimen. Our little girl, however, had always disliked meat and kept to her vegetarian principles. During the whole of the last year she had had as her daily diet only potatoes, one egg, one banana, one-half glass of milk, a little bread, biscuits and oleomargarine and about three or four times a week she ate vegetables and an apple or orange.

The family history was irrelevant.

On *physical examination* the girl was thin but of normal size. Her length was 1.50 meters, her body weight 35.3 kg. The secondary sex characteristics were normal for her age; there was no infantilism. She had a marked pallor with lemon-yellow tinge; skin and hair were dry. Her teeth were in bad condition, the tongue was somewhat smooth. Heart and lungs were normal. The spleen was palpable under the left costal margin. There were no further abnormalities referable to the abdomen. Roentgen ray examination of thorax, bones, stomach, and intestines revealed nothing of importance. The temperature was subfebrile, varying between 37 and 38° C., the blood pressure was 115/65.

The urine contained a great excess of urobilin, but was otherwise normal. The patient had regular bowel movements once a day. The stools were formed, did not contain ova, parasites or occult blood. On microscopic

* Dr. Elte (Assistant Director Binnengasthuis, Amsterdam) informed us that the child at that time showed a hypochromic anemia and that the hemoglobin content on admission was 45%; on discharge, 55%. Treatment consisted of iron and cod-liver oil.

examination they contained some excess of fat and undigested starch. Chemical analysis after addition of one liter of milk to a mixed diet revealed the following figures:

Total Fat Content of Dried Feces	33.05%
Neutral Fat	9.0%
Soaps	21.05%
Fatty Acids	3.0%

(These figures in our experience are somewhat above the upper limit of the normal range for a child of this age.)

The fasting stomach contained no free hydrochloric acid. After a test meal of 400 cc. broth, free hydrochloric acid appeared; the highest values after 1½ hours were 13 free and 55 combined hydrochloric acid (Fig. 4). The amounts of gastric juice obtained were small and viscid, due to mucus. Microscopic examination revealed leukocytes.

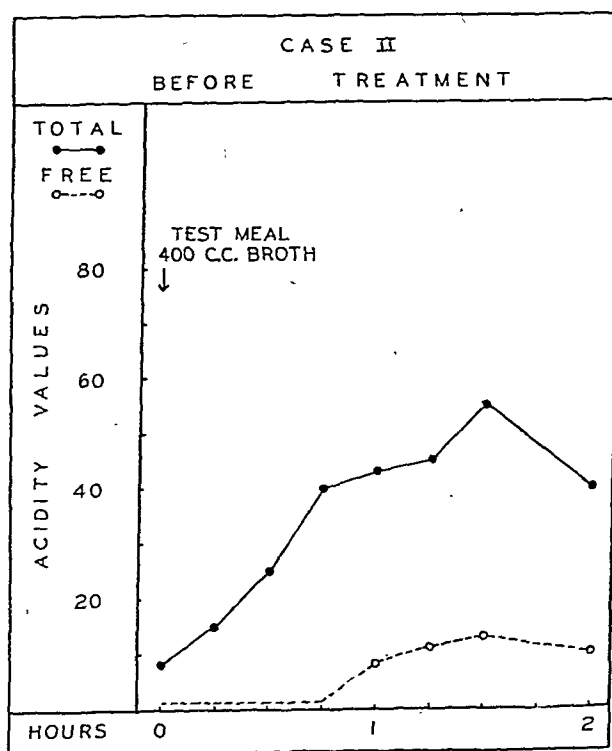


FIG. 4

The blood sugar tolerance curve was of a "flat" type: originating at a fasting value of 84 mg. %, the highest value obtained 1 hour after administration of 50 gm. of glucose by mouth was 108 mg. %.

Calcium and phosphate content of the blood were normal. The total protein, albumin and globulin content of the serum were normal; the cholesterol content was 129 mg. %. The van den Bergh reaction was positive indirect to an amount of 1.2 mg. per 100 cc. Reactions of Wassermann, Pirquet and Widal were negative.

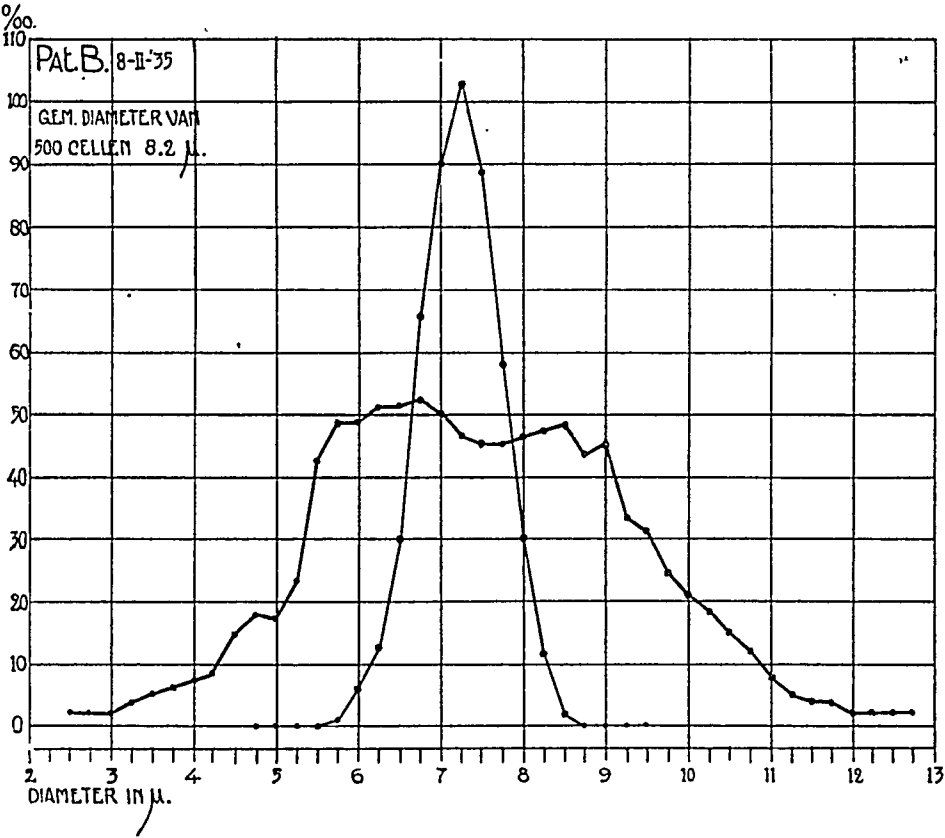


Fig. 5.—Case 2. Price-Jones curve.

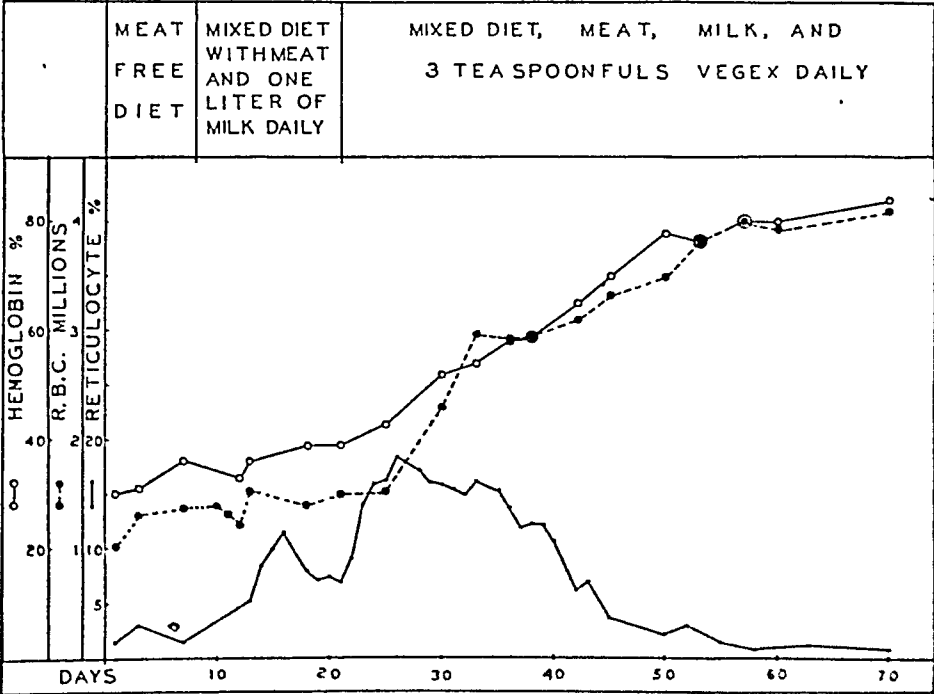


Fig. 6.—Case 2. The effect on the blood of administration of extrinsic factor to a patient with macrocytic anemia due to dietary deficiency.

The blood picture was as follows: hemoglobin 30% (Sahli), red blood cells 1,040,000 per c.mm.; color index 1.3. Number of leukocytes 2300 per c.mm.; blood platelets 70,000 per c.mm. Differential count: stabs 5%; polys 52%; eosinophils 1%; monocytes 7%; lymphocytes 35%; in addition the blood contained for every 100 white cells 2 normoblasts and 2 typical megaloblasts. The red cells showed a very marked anisocytosis, poikilocytosis, megalocytosis, and some polychromasia. The mean corpuscular volume on two occasions was 118 and 121 cubic micra. The Price-Jones curve is reproduced in Figure 5; the average cell diameter was 8.2 micra. The reticulocytes numbered between 1.5 and 3.0%.

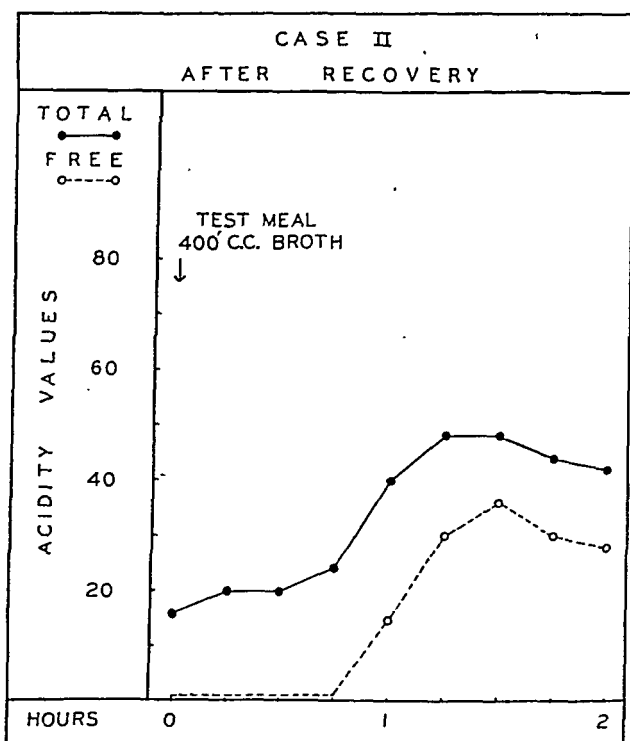


FIG. 7

After a control period on a meat-free diet, during which the blood findings did not change, the child was given a mixed diet containing plenty of meat, fruit, vegetables, and one liter of milk daily (Fig. 6). The number of reticulocytes rose to 14%, hemoglobin and erythrocytes to 39% and 1,500,000 per c.mm., respectively. On further addition of three teaspoonfuls of "Vegex" (a preparation rich in B vitamins) to this diet a second reticulocyte response was obtained: the reticulocyte count rising this time to 18.4%. Hemoglobin and erythrocytes increased rapidly; April 5, 2 months after her admission, the hemoglobin was 80%, the erythrocytes 4,000,000 per c.mm.; the Price-Jones curve had returned to normal and the excess of urobilin had disappeared from the urine.

A second gastric analysis now showed a completely normal curve. One and one-half hour after the test meal the acid values were 36 free and 48 combined hydrochloric acid. There was an abundant flow of gastric juice from the tube (Fig. 7).

After her discharge the patient was kept on a mixed diet. Her general and hematologic condition remained excellent as verified at a recent examination. Neither during the treatment nor after her discharge did she receive any liver or iron.

Discussion.—The common features in both these cases can be summarized as follows:

1. A history of a very defective diet, especially poor in meat, fresh milk and eggs over a prolonged period of time.

2. A clinical picture closely resembling that of pernicious anemia: a macrocytic anemia with increase of bile pigments in blood and urine, a smooth tongue, skin pigmentation and mental changes.

3. The presence in the stomach of free hydrochloric acid in small amount; the quantity of gastric juice secreted was small and contained mucus and leukocytes.

4. In the first case, the remission of the anemia initiated by liver has been sustained for the past 5 years solely on a mixed diet; in the other case, a complete remission was produced exclusively by a mixed diet that contained no liver but a rich supply of "extrinsic factor."

5. After treatment in both cases the gastric secretion improved and returned to normal; the amounts of gastric juice produced after the test meal increased, and the gastric juice contained less mucus, fewer leukocytes and a higher percentage of free hydrochloric acid.

6. A "flat" blood sugar curve.

In considering this syndrome a word may first be said about the differential diagnosis with regard to sprue or idiopathic steatorrhea (Gee-Herter's disease). So long as our knowledge of the etiology of the various forms of sprue is insufficient, we will lack a good definition of this condition which presents a wide range of clinical manifestations. It has been the experience of all investigators, however, including our own, that the one and never-failing sign in sprue is the fatty diarrhea. All other signs can vary or even be absent, but an abnormal content of fat in the stools, especially after addition of an extra amount of fat to the diet, appears to be characteristic. This is equally true for the tropical, non-tropical, and infantile variety. The cases here described definitely did not come under the heading of idiopathic steatorrhea, if the above criterion is applied.

The most usual classification given in the literature to cases of a similar type as just described seems to have been that of "pernicious anemia with presence of free hydrochloric acid in the stomach." In view of the newer (Castle) concepts of the etiology of pernicious anemia in the true (Addisonian) sense of the word, this description does not seem adequate. Addisonian pernicious anemia is considered a macrocytic anemia which is due to a lack of Castle's *intrinsic* factor in the stomach. The cases here under considera-

tion, however, appear to be due to a lack of *extrinsic* factor. They differ from classical pernicious anemia by the presence of free hydrochloric acid in the gastric contents and by their permanent cure by the intake of a mixed diet alone. Because of these characteristics, it seems as if our 2 cases were of the same type as those described by Wills³⁴ as "tropical" macrocytic anemia. It is to be stressed, however, that the designation "tropical" in this connection seems hardly warranted. The cause of the anemia, both in Wills' cases and in our own, was a deficient food intake. The social conditions in some tropical countries apparently lead to the intake of such a deficient diet by a larger group of the population than in Europe and in America. The resulting syndrome, however, is the same and not confined to the tropics. It should preferably be called, therefore, "macrocytic dietary deficiency anemia." The analogy between the anemia of our patients and the macrocytic anemia produced experimentally by a deficient diet in dogs and swine (Rhoads and Miller^{26,29}) also supports this contention.

The above considerations have led us to a new conception of some of the cases that have been described in the literature as "pernicious anemia with free hydrochloric acid in the stomach." A group of these cases has been critically reviewed lately by Alsted.² Upon reading over these case reports, one is impressed wherever details are given with the frequency of a history of deficient diet. It is of course possible that although free hydrochloric acid was present, Castle's intrinsic factor may still have been absent from the stomach in these cases so that a diagnosis of Addisonian pernicious anemia was justified. It is certainly at least as likely, however, that the defective diet, in other words, a lack of *extrinsic* factor was the underlying cause of the anemia. In Barnett's case⁴ this contention was proved by the daily administration of the patient's gastric juice mixed with beef to a test case of Addisonian pernicious anemia. A typical reticulocyte response followed. Unfortunately, we have not been able to carry out such an observation in our cases.

In the Thorndike Memorial Laboratory in Boston, one of us (J. G.) had the opportunity through the kindness of Dr. Thomas Hale Ham to see a similar case of "pernicious anemia with free hydrochloric acid in the stomach" with a history of very defective diet. In this case the daily administration of the patient's gastric juice with Vegex had provoked a reticulocyte response in a "test case" of true pernicious anemia. The patient herself recovered on a mixed diet only without any liver treatment.

The possibility of a lack of extrinsic factor as a *contributing* cause in Addisonian pernicious anemia may be considered in this connection. In some cases of this disease the history reveals the prolonged use of an unbalanced diet as a result of a peculiar preference of the individual for certain types of food and an aversion for others. In a number of Minot's and Cornell's cases, for instance, there had

been a remarkable low intake of meat, as opposed to a high fat consumption. It has been recognized for many years that after the disease is obvious there is often an aversion for meat and that the poor appetite aggravated by the illness may also give rise to a dietary deficiency. How far in the individual case of pernicious anemia the lack of intrinsic or of extrinsic factor or both have contributed to the development of the disease may be difficult to ascertain. It can, however, to a certain extent, be deduced from the dietary history and also from the reaction of the blood to the ingestion of a diet containing a potent source of intrinsic factor like meat or Vegex, but no liver. In this respect it might be suggested that in some of the cases described by Goodall¹⁶ and Ungley and James³³ where a macrocytic anemia reacted so well to intensive treatment with Vegex ("Marmite") a lack of *extrinsic* rather than intrinsic factor must have been the predominant cause of the anemia. This is also supported by the observations of Goldhamer and Isaacs¹⁵ who found some small amount of intrinsic factor in some cases of Addisonian pernicious anemia.

The low gastric acidity present in our cases and the improvement of the gastric secretion brought about by liver treatment in the first case and following a complete diet in the second case brings up the interesting point of a possible influence of dietary factors on gastric secretion.

Such an influence has been shown to exist experimentally by Cowgill and Gilman¹¹ who found a decreased secretion of hydrochloric acid from stomach pouches in dogs on a diet poor in the vitamin B complex. Miller and Rhoads²⁶ demonstrated that swine on a deficient (Goldberger) diet not only developed diminution of the secretion of hydrochloric acid but also of the blood-forming principle from their gastric juice. In man, several examples of damage to the gastric mucous membrane by a poor diet and of improvement by adequate dietary treatment can be quoted. Lindgren²² found a high incidence of achlorhydria among certain groups of the population of Sweden that partook of a "cereal and milk type" of diet. A history of a diet particularly poor in meat is often obtained from patients with "idiopathic" achlorhydria. Chester M. Jones, Benedict and Hampton¹⁹ with the aid of Roentgen rays, with the gastroscope and by biopsy during operations, found a severe gastritis in pernicious anemia, which essentially vanished in remission. Although there was no return of hydrochloric acid secretion, the mucous membrane of the stomach became much less inflamed than before treatment. A return of hydrochloric acid occurs not infrequently in patients with idiopathic achlorhydria with or without anemia if they are put on a well-balanced diet (Keefer *et al.*^{8, 20}). Lindgren²² made the same observation on some of his achlorhydric cases in Sweden. Even a return of hydrochloric acid in the stomach of patients with per-

nicious anemia, who had shown complete achylia before treatment, has been observed (see Alstéd). Castle, Heath and Strauss⁷ demonstrated the reappearance of intrinsic factor following liver therapy in a case of "pernicious" anemia due to multiple intestinal fistulae.

We do not know whether the deleterious effect of a deficient diet on the gastric mucous membrane is a specific result of the deficiency due, for instance, to the lack of a factor of the vitamin B complex or if it is simply a part of the general ill health of the body. The improvement of the gastric secretion during the treatment of the deficiency disease may be either specific like the disappearance of the tongue changes or may be nothing but a part of the return to general health of all the tissues as occurs during remission. Also the increased appetite and the regular intake of a normal diet containing an adequate supply of fluid and of the physiologic stimulants of the gastric secretion may be responsible for the improvement in gastric function (Lindgren²²; Rose, Stucky and Cowgill³⁰).

Both our cases also showed evidence of disturbed intestinal function: they had constipation and occasional diarrhea; in Case 2 the fat content of the stools on a diet containing 1 liter of milk a day surpassed the upper limit of normal; both had the "flat" type of blood sugar curve. It may be suspected, therefore, that their deficient diet had not only exerted an unfavorable influence on the gastric secretion, but had also affected the motility of the intestines and the absorption of digested material.

Just as for the stomach there are numerous indications that the function of the intestine, especially motility and absorption, may be impaired in dietary deficiency states. In pigeons, rats and monkeys dying from B deficiency a diarrhea during the last days of life can be observed regularly (MacCarrison²⁵). The same is found in dogs with black tongue disease (Chittenden and Underhill⁹; Goldberger, *et al.*¹⁴). At autopsy, the intestinal canal of these animals is edematous, in other parts atrophic, and contains mucus and blood. The occasional diarrhea of patients with idiopathic hypochromic and pernicious anemia, pellagra, and the severe diarrhea of sprue are probably all evidences of the intestinal disturbance associated with deficiency of some factor or related substance of the vitamin B complex. Mackie and Pound,^{24a} Mackie, Miller and Rhoads,^{24b} with the aid of Roentgen rays, have demonstrated the deranged intestinal motility in such cases. An impaired absorption of fat which is most marked in sprue can be detected to a minor degree in some cases of pernicious and in "idiopathic" achlorhydric anemia (Groen).¹⁷ The existence of impaired absorption suggests itself very often in those cases of pernicious anemia that require unusually large amounts of liver extract by mouth for their recovery or maintenance. Heath and Fullerton¹⁸ have shown that the absorption of potassium iodide is sometimes greatly delayed in dietary deficiency conditions. The increased tolerance to galactose in per-

pernicious anemia (Donath;¹² Singer and Wechsler³¹) has been ascribed to a slow absorption of this sugar from the alimentary canal. The "flat" blood sugar tolerance curve observed regularly in sprue (Thaysen³²) is also present in some cases of undernutrition, pernicious anemia, and allied deficiency disorders. As the blood sugar curve in those cases after intravenous administration of glucose is normal (van Andel and Groen¹), it may be assumed that the flatness of the curve after oral administration of sugar is caused by a retarded absorption of the glucose. Experiments carried out by one of the authors (J. G.), to be published elsewhere, have definitely demonstrated an impaired absorption of glucose in deficiency disease.

The gastro-intestinal disturbances shown by the 2 cases reported, namely, low gastric acidity, transient diarrhea, somewhat increased fat content in the stools, and flat blood sugar curve, make one wonder about the place of this clinical picture in the nosological system between pernicious anemia and sprue. For the reasons given above, the 2 patients suffered neither from the one nor the other of these diseases. Yet, the difference does not seem to be so much of a qualitative, as of a quantitative character. This, however, is equally true of the distinction between pernicious anemia and sprue and need not surprise us in view of the "floating" nature inherent to every deficiency disease. Thus, this "macrocytic anemia by dietary deficiency" is presented here, not so much as a walled-off entity but rather as a typical clinical picture intermediate between the other deficiency syndromes.

The deleterious effect of an impaired gastric and intestinal function on the progress of any deficiency disease has been pointed out by Castle^{5,7}. Not only is the diet in itself already poor in "accessory" food factors but the unfavorable condition of the intestine diminishes the actual utilization of even this amount. Both our cases in their downhill progress have shown such a vicious circle: namely, deficient diet, deficient state, poor gastric secretion and intestinal absorption, aggravated deficiency state. The same state of affairs can be observed in pernicious anemia and sprue. Thus, if one listens carefully to the history of a case of pernicious anemia or sprue, one is very often able to synchronize the relapses with a gastro-intestinal upset, a period of poor diet, or complicated infections, the remissions with a period of rest, better appetite and good food until finally the complete deficiency picture is established.⁷ It remains unknown what sets this vicious circle in motion. The clinical picture of the 2 cases described seems to have resulted entirely from a deficient diet. In the case of Addisonian pernicious anemia or sprue, however, important as the diet may be, it can hardly be the only causative factor.

Summary.—A clinical picture closely resembling pernicious anemia was observed in 2 cases where the history revealed a prolonged and pronounced dietary deficiency. Free hydrochloric acid

in subnormal amounts was found in the gastric juice. In 1 case, recovery induced by liver extract was maintained for 6 years on a complete diet alone without further liver treatment. In the other case, a complete remission was produced and maintained by the ingestion of a mixed diet containing plenty of meat, milk and a preparation of autolyzed yeast (Vegex) but no liver. Further features of the cases described included an improvement of the gastric secretion by the dietary treatment and a "flat" type of blood sugar curve indicating a poor intestinal absorption when the condition was severe.

It is suggested that the macrocytic anemia in these cases was due to a deficiency of Castle's extrinsic, rather than, intrinsic factor. Cases of this type which appear analogous to the "tropical" macrocytic anemia reported by Wills are probably more frequent than commonly believed. Many cases of so-called pernicious anemia with free hydrochloric acid in the stomach appear to belong to this group.

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THE SECRETION OF HIPPURIC ACID IN PERNICIOUS ANEMIA.

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We have previously reported^{3,6a} the findings in gastric juice and duodenal juice^{6b} of patients having pernicious anemia and attempted to correlate these findings with their clinical condition and the maintenance dose of liver required by them. Richter, Ivy and Kim,¹⁰ Wilkinson and Kline,¹⁴ and Goldhamer, Isaacs and Sturgis⁵ have demonstrated that the liver of untreated pernicious anemia patients did not contain the "active principle" of the liver while the liver of individuals not having pernicious anemia and treated pernicious anemia patients contained the "active principle." Wintrobe and Shumacker,¹⁵ VanDuyn,¹³ Goldhamer,⁴ Wright,¹⁷ and Rosenberg¹¹ have reported the presence of macrocytic anemia in patients with liver disease. Wintrobe¹⁶ has recently been able to experimentally produce macrocytic anemias in animals with severely damaged livers. In continuing the studies on maintenance dosage and the clinical condition of pernicious anemia patients, we therefore have studied the hepatic function of the patients as tested by excretion of hippuric acid in the urine following the ingestion of sodium benzoate. This test, as developed by Quick,⁹ is considered as a measure of the liver's capacity to furnish amino-acetic acid and as an index of its detoxifying power. Snell and Plunkett¹² recently concluded that "the results seem to indicate that the rate of synthesis of hippuric acid is a reasonably accurate and satisfactory test for the determination of parenchymatous hepatic damage." Kohlstaedt and Helmer⁷ concluded that the combined urea clearance and hippuric acid test is a reliable and valuable adjunct in the study of hepatic disease.

Methods. All but 2 of the patients on whom the tests were performed were typical clinically and hematologically of pernicious anemia. The patients have been followed in this department for varying periods of time up to 9 years. They have been classified as to age, degree of central nervous system involvement, presence of complications such as arteriosclerosis, infection, long-continued diarrhea, and the various degenerative

complications, kidney function as estimated by urea clearance, and the maintenance dose of liver extract required to maintain normal red blood cell count. The ones considered as to maintenance dosage of liver extract have been followed for at least a year, although the majority have been followed much longer. The patients able to maintain normal red blood cell counts while taking 3 vials of liver extract or 12 capsules of "Extralin" (Liver-Stomach Concentrate, Lilly) or less were considered as easy to maintain. Those requiring liver extract by injection were classified as difficult to maintain. The normal individuals tested were young, healthy adults.

On the day the test was run the patient's breakfast was limited to coffee and dry toast. Approximately an hour after breakfast 5.9 gm. of sodium benzoate was administered in a half glass of water by mouth to the patient. Quantitative urine specimens were collected at hourly intervals for 4 hours. The amount of hippuric acid in the 4 specimens was determined by the continuous ether extraction method of Quick.⁹ Van Slyke's⁸ method was used for the urea clearance determinations.

Results. The 10 normal individuals tested secreted an average of 3.15 gm. of hippuric acid in 4 hours. The amounts varied between 2.82 and 3.69 gm. The urea clearances of these individuals were normal (86 to 159% of normal, averaging 108.3%). A total of 51 examinations was run on 45 patients having pernicious anemia (Table 1). The average secretion was 2.59 gm. (1.16 to 3.89 gm.) per 4 hours. The average urea clearance for this group was only 77.8% of normal. The results of these examinations agree with the findings of Kohlstaedt and Helmer in that the kidney function, as shown by the urea clearance, influenced the amount of hippuric acid secreted in 4 hours. The average of the 21 examinations on 20 patients having urea clearances below 70% was only 2.4 gm. in contrast to the 2.8 gm. average for the 30 examinations on the 27 patients having urea clearances above 70%. Table 2 shows that only 5 of the 20 patients with urea clearances below 70% had a hippuric acid secretion above the lowest value found in the normal individuals. Four of these 5 had low blood counts when examined. The 2 patients whose urea clearance has been re-run after the blood has returned to normal now have normal urea clearances.

As shown by Tables 2 and 3, the red blood cell level did not seem to have a marked influence upon the amount of hippuric acid secreted, although there was a distinctly lower average urea clearance for the patients having low red blood cell counts.

There were, however, 4 patients who were examined both before and after an induced remission. Patient 22 had an increase in secretion of hippuric acid from 1.93 gm. up to 3.72 gm. This woman was in cardiac failure and in a very poor state of nutrition when first examined. The liver extended down 13 cm. from the costal border and generalized anasarca was present. The patient lost 38 pounds of fluid following the institution of liver extract therapy. When she was reexamined her blood was normal, the cardiac failure had disappeared, and she had gained 42 pounds.

The urea clearance had increased from 75 to 112%. The second patient (Case 21) had an excretion of 1.76 gm. when first examined and of 2.58 gm. when the blood was normal. There was only an increase in urea clearance of from 65 to 70%. This patient had gained 20 pounds between the examinations. Patient 35 showed only slight increase in excretion, although the urea clearance increased from 54 to 83% of normal. Patient 20, whose urea

TABLE 1.—THE HIPPURIC ACID SECRETION AND THE CLINICAL STATUS OF 45 PATIENTS HAVING PERNICIOUS ANEMIA AND 2 PATIENTS HAVING SIMILAR BLOOD PICTURES.

Case No.	Age, yrs.	R.B.C., millions	Hb., per cent.	Hippuric acid secretion, gm.	Urea clearance, %	C.N.S. involvement.	Complications.	Maintenance.*
1	60	4.70	97	2.23	69	—	+	D
2	07	5.46	101	2.72	82	+++	+	D
3	45	4.14	107	2.65	129	—	—	D
4	40	5.45	94	2.07	129	—	+	D
5	31	4.73	72	3.15	77	—	+	D
6	67	5.01	101	1.67	76	++	+	D
7	68	4.72	97	1.66	32	+++	+	D
8	61	5.57	129	2.89	84	—	+	E
9	69	5.45	106	2.55	55	+++	+	E
10	59	4.91	78	3.39	95	—	—	E
11	74	5.81	97	2.01	66	+++	+	E
12	41	5.45	111	3.35	156	—	—	E
13	43	5.40	97	3.41	72	—	—	E
14	70	5.65	113	1.62	126	+++	+	E
15	57	4.79	103	2.98	59	+	+	E
16	51	5.27	109	2.91	123	—	+	E
17	47	4.56	103	1.90	120	—	—	E
		5.01	104	1.83	116	—	—	E
18	63	4.74	106	2.70	108	+++	—	E
19	62	6.00	113	2.58	94	+	+	E
20	35	3.26	84	2.29	46	++	+	D
	36	5.00	86	1.89	45	++	+	D
21	56	2.19	65	1.76	60	+++	+	D
		5.41	113	2.54	70	+++	+	D
22	58	1.52	44	1.93	75	+++	++	?
		4.54	97	3.72	112	+++	++	?
23	50	4.22	67	1.16	72	+	+	D
	51	4.59	89	1.38	97	+	+	D
24	57	4.49	107	3.14	75	—	+	D
25	63	4.46	94	2.33	70	+++	++	?
26	63	3.64	82	2.46	65	+++	++	D
27	66	3.42	78	2.40	33	+++	+++	D
28	62	3.72	86	3.64	89	+	—	D
29	64	3.06	74	2.80	77	+	—	D
30	56	2.17	50	3.40	79	—	—	E
31	60	4.11	88	3.47	59	+	—	D
32	82	3.82	75	1.94	29	+++	++	E
33	63	2.85	76	2.92	60	+++	—	E
34	52	4.13	92	2.06	44	—	++	D
35	64	1.91	53	2.82	54	+++	+	D
		3.93	77	3.14	83	+++	+	D
		3.31	66	2.44	63	+++	+	?
36	67	3.31	66	2.44	63	+++	+	?
37	40	2.25	57	3.56	110	—	—	D
38	62	1.64	44	1.86	39	+++	+	D
39	66	2.95	79	2.06	51	+++	+	D
40	59	1.35	44	3.89	125	—	—	E
41	58	2.19	59	3.27	49	—	—	E
42	72	2.10	64	2.59	39	—	+	?
43	65	2.12	66	2.66	84	+	+	?
44	64	2.62	87	2.92	89	+	—	?
45	51	2.36	75	2.11	51	+	—	?
46	56	5.40	107	2.84	27	—	+	D
47	30	4.79	96	2.93	72	—	+	D

* D = difficult to maintain normal red blood cell count—i. e., require liver extract by injection.
E = easy to maintain normal red blood cell count on oral liver extract.

clearance was quite low (46% of normal) showed a slight decrease in hippuric acid secretion.

TABLE 2.—THE AVERAGE HIPPURIC ACID SECRETION OF 10 NORMAL INDIVIDUALS AND 45 PERNICIOUS ANEMIA PATIENTS WHEN CLASSIFIED AS TO THEIR CLINICAL STATUS.

	Number examined.	Average secretion of hippuric acid, gm.	Number of patients excreting >2.82 gm.	Number of patients excreting <2.82 gm.
I. Normals	10	3.15	10	0
II. Pernicious anemia patients	51	2.59	19	26
(a) With normal red blood cell count	25	2.56	9	16
(b) With red blood cell count not normal	24	2.62	9	15
(c) With normal urea clearance	27	2.80	14	13
(d) With urea clearance below 70%	20	2.40	5	15
(e) With early or no cord involvement	26	2.89	15	11
(f) With moderate to advanced cord involvement	19	2.35	3	16
(g) Under 60 years of age	20	2.91	13	7
(h) Over 60 years of age	25	2.49	6	19
(i) With no arteriosclerosis or other complications	18	3.00	12	6
(j) With arteriosclerosis or other complications	27	2.43	6	21
(k) Easy to maintain with normal red blood cell count	17	2.80	10	7
(l) Difficult to maintain with normal red blood cell count	21	2.53	6	15

TABLE 3.—THE AVERAGE HIPPURIC ACID SECRETION OF 10 NORMAL INDIVIDUALS AND OF 27 PERNICIOUS ANEMIA PATIENTS HAVING NORMAL UREA CLEARANCE.

	Number of patients.	Average secretion of hippuric acid, gm.	Number of patients excreting >2.82 gm.	Number of patients excreting <2.82 gm.
I. Normals	10	3.15	10	0
II. Pernicious anemia patients	27	2.80	14	13
(a) With normal red blood cell count	19	2.67	8	11
(b) With red blood cell count not normal	10	2.91	6	4
(c) With early or no cord involvement	19	2.93	12	7
(d) With moderate to advanced cord involvement	8	2.56	2	6
(e) Under 60 years of age	15	3.00	10	5
(f) Over 60 years of age	12	2.64	4	8
(g) With no arteriosclerosis or other complication	13	3.10	8	5
(h) With arteriosclerosis or other complications	14	2.60	6	9
(i) Under 60 having no or early central nervous system involvement and no complications	9	3.19	7	2
(j) Easy to maintain with normal red blood cell counts	12	2.94	8	4
(k) Difficult to maintain with normal red blood cell count	12	2.53	5	7

When the patients were grouped as to their clinical condition (Tables 2 and 3) it can be readily seen that those over 60 years, those having more advanced central nervous system involvement, and those having more advanced arteriosclerosis, infection, or diarrhea of long standing had distinctly lower average hippuric acid secretion than those not having these complicating factors. This applies both to the patients with these complications having low and to those having normal urea clearances. The 9 patients who

had a normal urea clearance and none of the above complicating factors had average secretions of 3.19 gm. per 4 hours. This is identical to the average of the normals. The 9 patients with at least four complications, including low urea clearance, averaged 2.15 gm.

Beebe and Lewis,¹ and Fouts and Zerfas² have shown that the older patients, the patients having more advanced cord involvement, the patients having a greater degree of arteriosclerosis, and those having infectious complications require more liver extract to maintain a normal red blood cell count than those not having these complications. As shown above, these complications are associated with lower average hippuric acid secretion. The patients difficult to maintain naturally, therefore, had a lower average hippuric acid secretion than the ones who could maintain a normal red blood cell count while taking oral liver therapy. It cannot be definitely shown, however, that in any of the patients examined a decreased liver function, as evidenced by a low output of hippuric acid, is the sole cause of the increase in requirement for liver extract. Patient 23 maintains a red blood cell count slightly below 4.5 million most of the time in spite of oral and parenteral therapy. The presence of a very low hippuric acid secretion in this case is suggestive that poor liver function is the cause of this. However, she gives a history of long-standing urinary infection. When first examined she could not gain weight and did not feel up to par. The urea clearance was only 72% of normal. When reexamined, she had gained weight and felt much better. The urea clearance had increased to 97% of normal. The hippuric acid secretion, however, had only increased from 1.16 to 1.38 gm. The red blood cell count remains at about the same level. Patient 17 is the only one having no known complications and normal urea clearance who has a very low (1.87 gm. average) hippuric acid secretion. He has maintained a normal red blood cell count on oral therapy for the 3 years that we have followed him. During the preceding 4 years he apparently had been able to do very well when he took liver extract regularly. Only 2 of the patients having no known complications cannot maintain a normal red blood count on oral liver therapy. Their hippuric acid secretion was 2.65 and 3.89 gm. Patient 40 secreted 3.89 gm. of hippuric acid when in blood relapse. After the red blood cell count reached normal he developed a catarrhal jaundice. There was no apparent increase in requirement of liver extract, but the secretion of hippuric acid decreased to 1.69 gm. Patients 46 and 47 (not included in Tables 2 and 3) give a history of long-continued diarrhea and have had blood pictures similar to that seen in pernicious anemia. They both have free acid in the gastric contents, yet require liver extract by injection to maintain normal red blood counts. Their hippuric acid secretions were 2.84 and 2.93 gm. respectively.

Discussion. It is evident that there is no marked dysfunction of the power of the liver of pernicious anemia patients to conjugate benzoic acid. Their secretion of hippuric acid, however, varies with their general condition. As has been previously shown, the patients with poor kidney function secrete smaller amounts of hippuric acid than those with normal function. In a paper in press it will be shown that the older patients, the patients having advanced cord involvement, infection and the degenerative complications are more apt to have lower urea clearances than the pernicious anemia patients who do not have these complications. However, even in the patients in the above groups who do have a normal kidney function there is a decrease in the secretion of hippuric acid. The patients who have these complicating factors have previously been shown to require more liver extract.

Conclusion. In general, it can be assumed that the decrease in secretion of hippuric acid in pernicious anemia patients and the increase in requirement of liver extract are both the result of the complicating factors. Decreased liver function, as estimated by the ability of the liver to conjugate benzoic acid, was not shown to influence the requirement of liver extract.

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THE LEUKOPENIC INDEX.

WITH REFERENCE TO NORMAL WHITE BLOOD CELL VARIATIONS.

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THE leukopenic index was introduced by Vaughan,^{10a,b} in 1934, as a new diagnostic procedure in allergic diagnosis to supplement the usual skin tests, trial diets and clinical methods. Since the initial

communication the clinical application and value of the leukopenic index has been clearly demonstrated in a number of reports. Vaughan^{10c} found that the procedure facilitated more accurate diagnosis in food allergy. Rinkel^{6a,b,c} has reported concerning its value in infantile eczema, intractable food allergies, and as a diagnostic aid. Gay² utilized the leukopenic index in the diagnosis and treatment of peptic ulcer, and Zeller¹² has found it of value in the diagnosis and treatment of intractable asthma.

Vaughan's communications state briefly that a food to which a patient is sensitive will produce a postingestive leukopenia, whereas a food not productive of symptoms will produce a leukocytosis, but the cell decrease or increase should exceed 1000 cells or more before one could regard the response as significant. Rinkel and Gay⁷ have described the more important types of postingestive white blood count food curves together with their clinical interpretation. A number of questions have arisen, however, relative to the reliability of the fundamental basis of the test.¹

Sabin, Cunningham, Doan and Kindwall⁸ report "marked fluctuations in the total leukocyte count in the fasting, resting state when counts were made at intervals of fifteen minutes," but attention should be called to the fact that 3 of the 6 experimental subjects continued their usual laboratory activities throughout the course of the experiment, and 3 others ingested food during the test period. Medlar,⁴ on the basis of white blood counts performed at 3- and 5-minute intervals on 3 subjects, reports wide variations of the counts, but does not state whether food, drink or exercise was permitted during the course of the experiment. Simpson,⁹ who reports continuous variation in leukocyte counts, describes his conditions of experiment including subjects "of about the same age and working under much the same conditions as the staff of the Radiological Department except that they were not exposed to radiation." In Washburn's¹¹ series of white blood cell counts on infants he reports hourly fluctuations, but attention should be directed to the fact that the subjects were kept on the usual foods and routine.

The reliability of these various reports is not questioned, but in view of the fact that the studies were done under wholly different conditions than the leukopenic index white blood cell counts, they cannot be accepted as a basis for refuting or even raising a question as to the reliability of leukopenic index studies. Jones, Stephens, Todd and Lawrence³ state that "under basal conditions, the total number of white blood cells in normal subjects shows only slight variations." In their series the 2 cases presenting wide fluctuations were afflicted with respiratory infections but the remainder did not exceed fluctuations beyond 1500 cells. Ponder, Saslow and Schweizer⁵ state that "an afternoon rise was not regularly observed; indeed the white cell count frequently remained at a constant level throughout the day."

The purpose of this communication is to present studies revealing white blood cell responses under various conditions, and to point out the reasons for the apparent discrepancies of the leukopenic index as indicated by previous reports on white blood cell responses.

There are two fundamental important procedures in obtaining accurate blood studies for leukopenic index determinations.⁷ First is the preparation and control of the patient, and second is making the blood studies under uniform conditions.

The patient is instructed to eat a light supper and to obtain a good night's rest with instructions to report at 8 or 9 A.M. without food, drink or smoking. He is seated for a hour in a room maintained at constant temperature and told to relax, and be at ease as much as possible avoiding conversation with other patients and all unnecessary movements throughout the entire test period. Following the initial rest period a fasting white cell count is done, after which the test food is immediately eaten, taking care not to take more than 3 to 5 minutes to do so. Until one is familiar with the test it may be advisable to perform 2 fasting counts at 10-minute intervals. Subsequent white cell counts are then done at 15- to 20-minute intervals until the curve reflects adequately the nature of the food response. It should be emphasized that the patient is to maintain absolute rest and quiet during the course of the test.

The technique of the count is as follows: a sharp lancet is used to obtain a free flow of blood from the finger, the same pipette is used for a given serial count, and to obtain equal and uniform dispersion of the cells the pipette is shaken in the same manner and period of time for each count. After discarding the first drop of blood the second and third are placed in the counting chamber and after several minutes elapse to permit complete settling of the cells, counts of the 8 squares are made and recorded. Precautions to keep the pipettes perfectly clear are essential. The presence of a thin film noted by dark discoloration of the pipette lumen may be eliminated by cleansing with alcohol and nitric acid.

This study includes serial white blood cell counts taken on 10 individuals under various conditions. The resting counts in 8 instances were done by preparing the subjects in the manner already described. The white blood cell counts taken after violent exercise included in each instance running up and down 6 flights of stairs. Under "mild activity" are recorded counts taken while the individual was performing routine office and laboratory work. In 5 subjects serial counts were performed following heavy meals including soup, full meat and vegetable courses, dessert and a drink, while in 2 others counts were done after light meals consisting of 1-pint of milk and 2 crackers. In the allergic individuals there were no foods given to which there was a sensitization.

The white blood cell counts taken at intervals under conditions of rest and fasting over extended periods varying from 45 minutes to $3\frac{1}{2}$ hours reveal fluctuations of 200 to 750 cells. Any single series of counts, however, will show a consistently basic level, with an occasional departure of a count from this level. It is these counts which account for the wider fluctuations, but even these are well within the limit of 1000 cells which Vaughan gave as the range of variation before a count should be regarded with import. In the usual positive leukopenic index it is necessary that in addition to a drop in the white cell count there must be sustained or even further drop in this count when continued at intervals. Variations such as presented in this rest and fasting series remain close to the basic counts, and do not resemble a positive leukopenic index. A positive leukopenic index reveals definite types of fluctuations characteristic of sensitization. Control fasting and resting counts when

TABLE 1.—WHITE BLOOD COUNT STUDIES ON 10 INDIVIDUALS.

Condition of patient.	Case.	Number of counts made.	Length of time of counts (hrs.)	Range of W. B. C.	Range of W. B. C. fluctuation (cells).
Fasting and resting . .	1	3	$\frac{1}{4}$	7400-8050	650
	2	5	$1\frac{1}{4}$	4900-5400	500
	3	5	$1\frac{1}{4}$	5300-5500	200
	4	4	1	3850-4100	250
	5	14	$3\frac{1}{2}$	5800-6400	600
	8	12	3	5800-6500	700
	9	8	2	4800-5300	500
	10	7	$1\frac{1}{4}$	5400-6150	750
Mild activity .	1	5	$1\frac{1}{4}$	8700-8800	100
	4	4	$1\frac{3}{4}$	4400-5900	1500
	6	7	$2\frac{1}{2}$	5500-7400	1900
	7	4	1	3800-6200	2400
Violent exercise	2	4	1	5300-6900 (returned to normal in 30 min.)	1600
	2	4	1	5300-7100 (returned to normal in 15 min.)	1800
	4	4	1	4100-5900 (returned to normal in 15 min.)	1800
After light meal and rest . .	2	3	$\frac{1}{4}$	4900-6700 (returned to normal in 1 hr.)	1800
	9	10	3	5000-7600 (returned to normal in $2\frac{1}{4}$ hrs.)	1600
After heavy meal . . .	1	7	$1\frac{1}{4}$	9100-13,100 (returned to normal in 1 hr.)	4000
	3	4	3	5100-8400 (returned to 6300, 3 hrs. later)	3000
	4	8	$2\frac{1}{4}$	3800-8900 (returned to 4400, $2\frac{1}{4}$ hrs. later)	5100
	5	5	$2\frac{1}{4}$	6200-9800 ($2\frac{1}{4}$ hrs. later 7200)	3600
	6	3	$2\frac{1}{4}$	7900-10,300 ($1\frac{1}{4}$ hrs. later 8400)	2400

TABLE 2.—WHITE BLOOD COUNT STUDIES ON 10 INDIVIDUALS.

Time.	Case 1.*	Case 2.*	Case 3.*	Case 4.†	Case 5.*	Case 6.†	Case 7.†	Case 8.†	Case 9.†	Case 10.†
9.15 A.M.				4,050 R						
9.30	8,050 R		5,300 R	3,900 R					5,300 R	6,150 R
9.45	7,900 R		5,400 R	3,850 R	6,400 R				5,200 R	6,000 R
10.00	7,400 MA		5,500 R	4,100 R	6,400 R					
10.15	9,300 MA		5,500 R	5,900 VE	5,800 R	5,500 MA	3,800 MA	6,100 R	5,100 R	6,050 R
10.30	8,700 MA	5,200 R		3,850 R		5,800 MA	3,200 MA	6,000 R	5,300 R	6,000 R
10.45	8,800 MA	5,400 R		3,900 R		6,400 MA	5,900 MA	6,200 R	4,800 R	5,400 R
11.00	8,800 MA	4,900 R	5,400 R	3,750 R	6,200 R	7,400 MA	6,200 MA		4,700 R	5,900 R
11.15	8,700 RH	5,000 R		HM				5,800 R	5,200 R	5,400 R
11.30	8,800 RH	5,300 R			5,800 R	6,700 MA		6,400 R	5,000 R	6,000 R
11.45	8,800 RH		HM	8,900 R				6,500 R	LM	
12 NOON				6,000 R						
12.15 P.M.				5,950 R				6,300 R		
12.30	8,500 RH	VE	8,400 R	5,040 R	5,900 R	6,400 MA	LM	6,400 R		
12.45	9,100 RH	6,900 R		5,020 R		6,900 MA		6,500 R	6,000 R	
1.00	HM	6,100 R			6,250 R		7,600 MA	6,500 R	6,200 R	
1.15		5,100 R		4,800 MA				6,500 R	7,600 R	
1.30		4,900 LM			6,200 R			6,300 R	7,000 R	
1.45	13,000 R	6,700 R		4,400 MA	HM			6,800 R	6,700 R	
2.00	12,300 R	5,800 R		5,450 MA		LM		6,300 R	6,800 R	
2.15	11,300 R	5,300 VE		5,900 MA				6,300 R	6,300 R	
2.30	10,000 R	7,100 R	6,700 R		9,800 R	7,900 MA		5,900 R	5,900 R	
2.45	9,700 R	5,300 R						5,400 R	5,400 R	
3.00	9,000 R	5,100 R	6,600 R	5,650 MA	6,700 R	6,100 MA	6,500 MA		4,600 R	
3.30			6,300 R		8,200 R	6,900 MA				
4.00					7,200 R	HM	6,800 MA			
6.30						10,300 MA				
8.00						8,400 MA				

* Non-allergic

† Allergic

 R—Resting
 RH—Resting plus Heat
 MA—Mild Activity

 HM—Heavy Meal
 VE—Violent Exercise
 LM—Light Meal

plotted reveal practically a straight line without a sustained increase or decrease in the counts, whereas the usual leukopenic index will not only reveal striking decreases in white blood cells totaling as high as 4500 cells, but this decrease will be sustained through variable periods.

The influence of a heavy meal is noted in 5 instances showing increases of white blood counts varying from 2400 to 4800 cells, but gradually returning to the pre-prandial status in 1 to 3 hours. Light meals taken after a resting period resulted in increases of 1800 to 2300 white blood cells with a gradual return to the basic count in from 1 to $1\frac{3}{4}$ hours.

In 3 instances violent exercise resulted in immediate elevation of the counts varying from 1600 to 1800 cells. This increase was of a transient character as the basic level was reached again in 15 to 30 minutes. Mild activity over periods of 60 to 75 minutes resulted in white cell fluctuations from 500 to 2400 cells.

Summary. Serial white blood cell counts taken under resting and fasting conditions reveal consistently uniform counts with variations not exceeding 750 cells. The larger variations are infrequent, and for the most part the counts are within 200 to 300 cells of one another.

The influence of mild and violent exercise is noted by definite white cell increases with a return to the pre-exercise period within 30 minutes.

Heavy and light meals result in white cell responses increasing in proportion to the quantity of food ingested and sustained in gradually decreasing numbers for as long as 3 hours.

Previously reported work on white blood cell responses used as a criterion for questioning leukopenic index studies cannot be accepted as a basis for evaluation, since the conditions of experiment were dissimilar.

Clinical evidence, previously reported work, and the present studies appear to substantiate the leukopenic index as a new and valuable aid to supplement the usual methods of diagnosis in allergic studies.

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A CHEMICAL PECULIARITY OF PELLAGRA BLOOD.*

SECOND REPORT.

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IN a preliminary note,¹ the author reported observations relative to the phenomenon of rapid iodine decolorization by the erythrocytic mixture of pellagra blood. In that study it was found that under a standard technique, pellagrous blood reduced iodine solution at a constantly greater rate in comparison with normal controls and in comparison with samples from a variety of non-pellagrous pathologic conditions. It was proposed that this reaction might be of clinical value in the diagnosis of pellagra.

During the past 4 years, further confirmatory work has been done, but this report deals with a study of the modification in technique advocated by Sotelo² in 1935. This modification in technique is essentially that of stirring the erythrocytic coagulum with a glass rod immediately upon adding the alcohol-ether mixture. The Lugol solution is then added in 1 hour. Five hours later, the tubes are compared with the standards. The interpretation of the test is as previously reported. The glass rod may be removed without adhesion of any particles after the mixture is thoroughly stirred. The mixture is stirred until it becomes a fine, granular mass. By this technique, the total time involved in the test is therefore 7 hours, in comparison with 19 hours by the former procedure.

This modified technique and the original method were used on 52 cases with normal controls; 17 of these cases had classical symptoms of pellagra at the time of testing. In all, excepting 1, the tests were positive, ranging from mild to severe. Of 8 untreated cases, 7 gave severe reactions, and 1 a moderate reaction. One case which had classical symptoms of dermatitis, diarrhea and glossitis gave a negative reaction. This patient had been under treatment with yeast and pellagra diet intermittently for about a year, and had been taking yeast daily for about 3 weeks prior to the time of the test. It is believed that this latter fact had some bearing on the negative reaction. However, treated patients with active symptoms of pellagra have always, with the above exception, given positive reactions.

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There were 8 cases with definite, classical symptoms of pellagra at the time of the test who had been under treatment varying from 1 to 3 months. These all gave positive reactions, ranging from mild to severe by the original method, and from mild to moderate by the Sotelo modification.

In this series, there were 3 pellagrins who had formerly been confined as inmates of mental hospitals with the diagnosis of "psychosis with pellagra." The duration of treatment on these ranged from 3 to 5 years. They had consulted the physician with complaints consisting chiefly of "nervousness, general weakness, loss of appetite, and insomnia." One of these patients had mild mental symptoms. The test was run because of the history of pellagra. In all 3 of these the tests were positive.

TABLE 1.—COMPARISON OF ORIGINAL TEST AND SOTELO MODIFICATION.

	Iodine decolorization.	Sotelo modification.	No. of cases.
<i>I. Those cases giving positive reactions:</i>			
A. Definitely diagnosed, untreated, classical cases of pellagra	Severe	Severe	7
	Moderate	Moderate	1
B. Definitely diagnosed, treated pellagra; symptoms present at time of test	Mild to severe	Mild to moderate	8
C. Cases treated over several years (past history of psychosis with pellagra; vague nervous and mental symptoms at time of test)	Mild	Mild	2
	Moderate	Moderate	1
<i>II. Those cases giving negative reactions:</i>			
A. Treated pellagra; symptom-free at time of test	Negative	Negative	11
B. Definitely diagnosed pellagra, treated, but with classical symptoms present at time of test	Negative	Negative	1
C. Suspected pellagra:			
1. Asymptomatic, and tested solely because of mal-nourished appearance	Negative	Negative	9
2. Suspected because of certain symptoms present. Final clinical diagnoses were:			
Cholecystitis	Negative	Negative	1
Hypertension and nephritis	Negative	Negative	1
Pulmonary tuberculosis	Negative	Negative	1
Chronic salpingo-oöphoritis	Negative	Negative	3
Carcinoma of stomach	Negative	Negative	1
Pernicious anemia	Negative	Negative	1
C.N.S. lues	Negative	Negative	1
Psychosis with cerebral arteriosclerosis	Negative	Negative	1
Undiagnosed	Negative	Negative	2
Total			52

Eleven cases of treated pellagrins who were symptom-free at the time were tested. In each of these a definite diagnosis of pellagra had been made at the time of illness. Treatment ranged from 8 months to 3 years. In all of these, the reactions were negative.

There were 21 cases of suspected pellagra. The disease was suspected in 9 individuals solely upon the basis of existing malnutrition. These people were residing in a community camp and volunteered to have the test performed. They had no symptoms of active pellagra at the time. The reactions to the tests were all negative. There were 12 cases in which pellagra was suspected because of the symptomatology. The tests were performed as a means of excluding the diagnosis of pellagra. Dermatitis was not present in any of these cases. Symptoms which led to the suspicion of pellagra were: diarrhœa and mental changes. The accompanying Table 1 reveals the final clinical diagnoses.

The modified technique was compared with the original in each case and it was found to be much more rapid, but not so highly differentiating. That is to say, in general, the reactions by the modified technique were very rapid, and in some cases, the color difference was not so great as in the original procedure. It is found that the amount of decolorization of the iodine varies with the room temperature. The rapidity of iodine decolorization in all samples is proportionately greater with an increase in room temperature. It is noted that, by the new technique, in cases of severe pellagra, the test may be read within 2 hours after the iodine is added. It is important to develop a constant technique of stirring the erythrocytic coagulum so that the texture is the same in the control and the patient.

No explanation for this phenomenon of relatively rapid iodine decolorization by the erythrocytic mixture of pellagra blood can be offered by the author at the present time. Work is being done toward this end, but as yet, no conclusive data have been acquired.

Conclusions. The modification in technique advocated by Sotelo is of definite value as a time-saving procedure. It is not so highly differentiating as the original method because of the increased rapidity of iodine reduction which takes place in both the normal and pellagra specimens, resulting in a less-striking difference in color change when compared with the standards. Our experience continues to show that the erythrocytic mixture of pellagrous blood reduces iodine more rapidly than normal or other pathologic specimens.

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PAREDRINE (β -4-HYDROXYPHENYLISOPROPYLAMINE).**A CLINICAL INVESTIGATION OF A SYMPATHOMIMETIC DRUG.***

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PAREDRINE (the name which has been applied to β -4-hydroxyphenylisopropylamine) was first described in the literature of the German patent office in 1913,⁴ but has aroused little interest since that time. It belongs to the class of sympathomimetic drugs both on the basis of its chemical structure (Fig. 1) and of its behavior in animals.^{1,2} The common drugs of this type produce so many simultaneous effects that their use for any specific purpose is limited. On the chance that paredrine allied as it is, on the one hand, to epinephrine and on the other, to ephedrine, might possess some of the characteristics of this group to an intensified degree and others, if at all, only to a slight extent, we were led to determine more extensively its action in man. Our purpose has been not so much to treat disease as to study the reaction of the normal adult to the drug; nevertheless, when the presence of certain diseases enabled us better to demonstrate specific effects of the drug, we have used suitable patients. Several series of studies differing widely in method have enabled us to formulate a more or less complete picture of the usual response of the individual as a whole to paredrine in various dosages, and to observe the occasional unusual reactions.

Material and Methods. The subjects upon whom these observations were made may be grouped as: 1. healthy individuals, usually medical students; 2, hospital patients subject to illnesses not affecting the experiments; and, 3, patients whose pathological physiology was such as to suggest that a sympathomimetic drug might affect it. Both sexes were included but the extremes of age avoided.

In the main, routine methods of clinical examination served for a study of the effects of the drug on the heart, the pulse, the blood pressure, the urine flow, the pupils, the nasal mucosa and on the duration of local anesthesia of the skin. In addition, certain special studies were made, including those on intraocular tension by a Schiötz tonometer, on the movements of the small intestine by an intrainestinal balloon system³ and by fluoroscopy after an opaque meal, and on skin temperature changes as determined by a thermocouple-galvanometer system.

RESULTS. I. Systemic Administration. A. Effects of Single Doses.
1. ON THE CARDIOVASCULAR SYSTEM. (a) *Blood Pressure:* Paredrine caused a rise in blood pressure (Table 1) when 10 to 20 mg. were

* Aided by a grant from Smith, Kline & French Laboratories.

injected subcutaneously or when 20 to 40 mg. were given by mouth. Larger doses up to 40 mg. subcutaneously and to 60 mg. by mouth were used in some instances, but occasionally produced unpleasant symptoms; smaller doses were ineffectual. Only one unpleasant reaction occurred within the ordinary range of dosage. Orally administered, paredrine as compared to ephedrine produced its effect more rapidly, but acted for a shorter time (Fig. 2); injected, paredrine likewise acted more quickly than epinephrine, but it maintained its action for a longer period (Fig. 3).

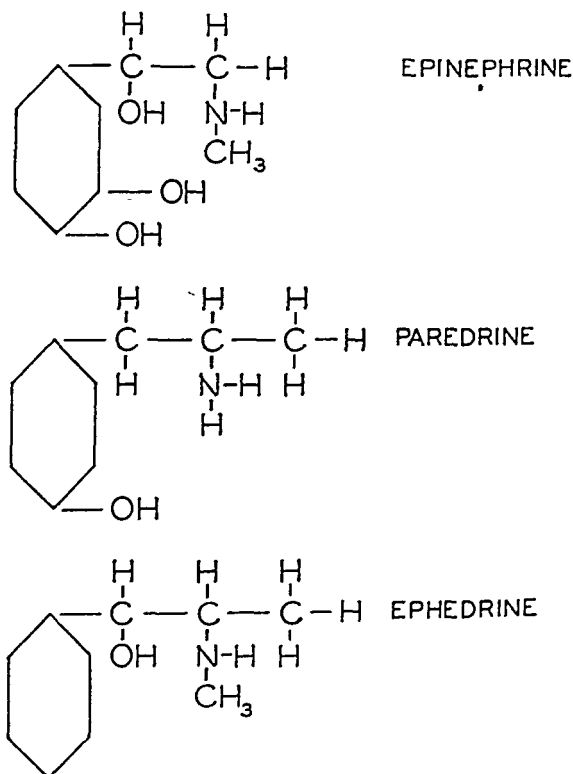


FIG. 1.—The chemical relationship of paredrine to epinephrine and to ephedrine.

(b) *Cardiac Mechanism:* The heart rate decreased as the blood pressure rose in almost every case (Table 1, Figs. 2 and 3). The rhythm was occasionally altered, extrasystoles appearing not infrequently, while in two instances a persistent coupling of the beats occurred during the height of the blood pressure rise: once in a case of Addison's disease and once in a normal young woman of 21. Systolic murmurs and splitting of the heart sounds often accompanied the rise in blood pressure.

(c) *Skin Temperature:* The temperature of the skin over the toe pulps of 13 normal individuals was tested after oral doses of 20 to

TABLE 1.—THE OBJECTIVE AND SUBJECTIVE EFFECTS OF SINGLE DOSES OF PAREDRINE.

Case.	Age.	Sex.	Diagnosis.	Signs.			Symptoms.	
				Rise in blood pressure.		Heart sounds.		
				Sys- tolic (mm.)	Dias- tolic (mm.)			Change in pulse.
				Dura- tion (mins.)				
By Mouth—10 mg.								
C. H.	26	M.	Normal	0	0	0	No change	None.
W. W.	16	M.	Chronic prostatitis	0	0	0	None	None.
M. S.	12	F.	Chorea	0	0	0	None	None.
By Mouth—20 mg.								
T. F.	50	M.	Renal disease	24	6	75	Systolic apical murmur	None.
A. C.	59	M.	Hypertension	60	20	140	Louder	None.
D. H.	47	M.	Asthma	0	0	0	None	None.
A. D.	43	F.	Gastric neurosis	16	10	90	None	None.
R. W.	32	M.	Asthma	0	0	0	Possible clearing of asthmatic riles	Subjectively feels better.
By Mouth—10 mg.								
M. A.	17	M.	Duodenal ulcer	60	30	105	No change	Mild palpitation.
B. C.	27	M.	Duodenal ulcer	84	32	75	Louder, split second	None.
J. S.	26	M.	Subacute appendicitis	52	30	90	Split second—extrasystoles	Palpitation.
E. R.	30	M.	Buerger's disease	100	36	100	Systolic apical murmur	"Choky feeling."
E. R.	30	M.	Buerger's disease	94	28	140	Systolic apical murmur split second	Slight headache.
T. F.	21	M.	Diabetes	107	107	?	Slight headache.
J. C.	51	M.	Diabetes	36	0	75	No change	None.
I. P.	17	F.	Arthritis	32	10	140	Louder	Tightness in chest.
O. D.	30	M.	Encephalitis	51	24	95	Louder	Palpitation (mild).
G. R.	26	F.	Psychasthenia	18	8	110	Louder, pulse irregular	Palpitation perspiration.
B. R.	14	M.	Pyelitis	86	50	105	Louder, extrasystoles	Severe headache, sweating, nausea.
D. H.	17	M.	Asthma	6	0	?	None	None.
E. H.	64	M.	Carcinoma	82	16	95	None	Slight palpitation.
By Mouth—60 mg.								
C. H.	26	M.	Normal	62	40	90	No change	Palpitations.
O. D.	30	M.	Encephalitis	26	10	120	Systolic apical murmur split first	Palpitation (mild).
Subcutaneous—10 mg.								
C. M.	22	M.	Normal	38	22	90	None	Slight palpitation.
S. S.	52	M.	Arthritis	20	8	70	Louder	None.
W. R.	10	M.	Hysteria	30	8	85	Split first sound, split second sound	None.
Subcutaneous—20 mg.								
I. C.	16	M.	Asthma	64	30	105	Systolic apical murmur	Mild palpitation.
N. V.	78	F.	Undiagnosed anemia	50	20	75	No change	None.
N. P.	54	F.	Addison's disease	94	28	70	Coupled beats systolic apical murmur	Sweating, slight headache.
E. L.	...	M.	Arteriosclerosis	26	6	50	Slightly louder	None.
Subcutaneous—40 mg.								
C. H.	26	M.	Normal	48	38	120	No change	Slight constriction across chest.
J. C.	29	M.	T. B. adenitis	96	44	85	Systolic apical murmur split second, extrasystoles	Mild palpitation.
G. M.	59	M.	"	62	20	95	Systolic apical and basal murmurs	Mild throbbing pain in the head.
M. S.	22	F.	Migraine	60	24	20	No change	Severe headache, sweating, vomiting.
C. H.	23	M.	Normal	88	50	?	Systolic apical murmur extrasystoles	Vomiting, chills, severe headache.

60 mg. of subcutaneous doses of 10 to 20 mg. had been given. In 10, no definite change occurred; in 1, following an injection of 40 mg., the temperature fell slightly; in 2, after the injection of 20 mg., a definite rise took place. These observations confirm the impression one occasionally receives of a slight flush after paredrine, in sharp contrast with the usual pallor and fall in skin temperature

PAREDRINE AND EPHEDRINE. BLOOD PRESSURE AND PULSE CHANGES.

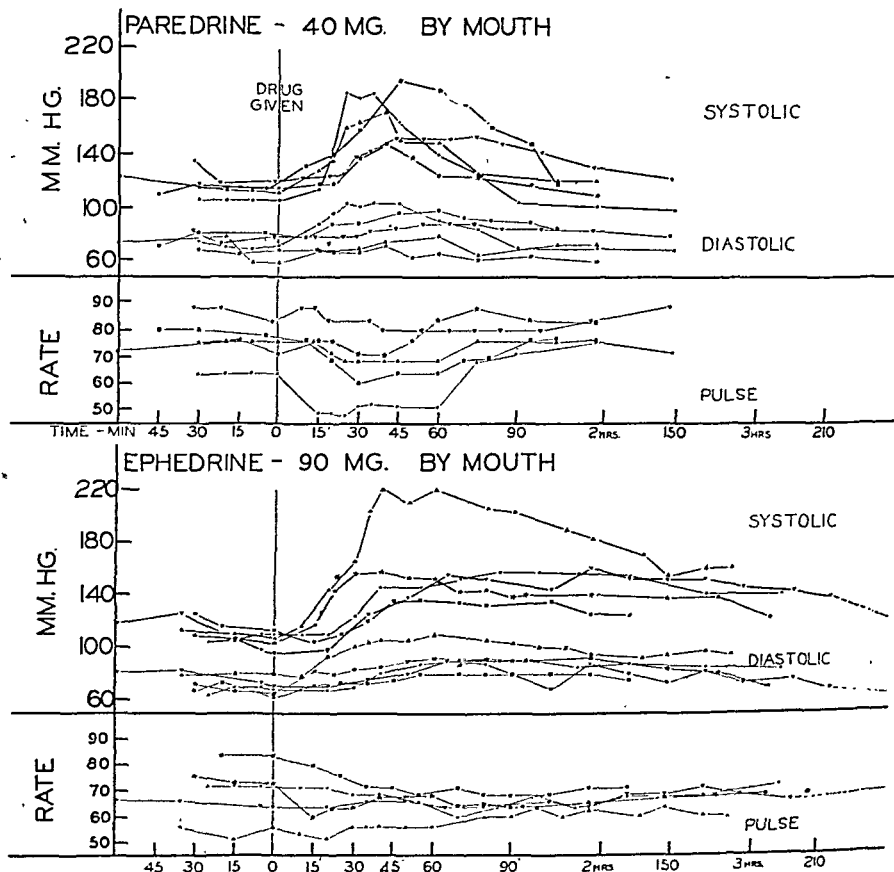


FIG. 2.—The comparative effects of paredrine and ephedrine upon the blood pressure. Effective doses of the two drugs were given by mouth to normal subjects. The results upon 5 unselected cases from each group are presented.

after epinephrine (Fig. 4). In 5 of 6 cases of Buerger's disease tested after paredrine, little change in skin temperature resulted; in 1 individual, 1 of 2 upon whom periarterial sympathectomies had been done, an oral dose of 40 mg. caused the skin temperature to rise abruptly (Fig. 5), in the diseased leg only. A similar result was subsequently obtained in this individual by 90 mg. of ephedrine. In both instances this rise in temperature coincided with the rise of blood pressure.

(d) *Urine Flow*: In 13 subjects the urine flow was measured for 2 hours before and for 2 hours after giving the drug. In each instance the fluid intake of the subject was restricted to a measured volume of water given hourly during the experiment. The volumes of the urine collection bore in general a direct relationship to the blood pressure changes (Table 2). Traces of protein were detected only twice during these experiments.

PAREDRINE AND EPINEPHRINE. BLOOD PRESSURE AND PULSE CHANGES.

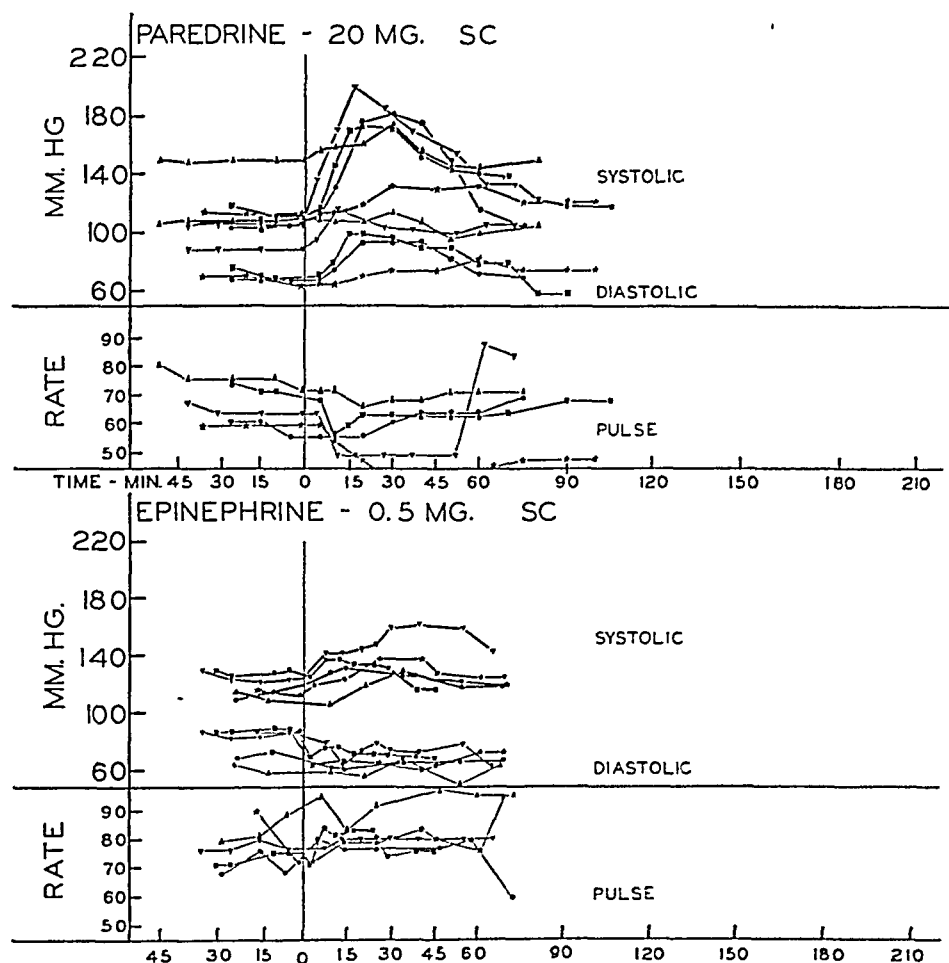


FIG. 3.—The comparative effects of paredrine and epinephrine upon the blood pressure. Effective doses of the two drugs were injected subcutaneously into normal subjects. The results upon 5 unselected cases from each group are pre-ented.

2. ON THE GASTRO-INTESTINAL SYSTEM. (a) *Subjective Symptoms*: Subjective evidence of the effects of paredrine on the digestive tract was notably lacking in all but 2 subjects. In these 2 severe reactions occurred, as will be described later. In no other instance was nausea, vomiting, abdominal distress or call to stool observed. (b) *Objective Evidence*: Two cases were studied by the balloon method. Kymographic tracings of duodenal contractions showed no

PAREDRINE AND EPINEPHRINE. SKIN TEMPERATURE CHANGES.

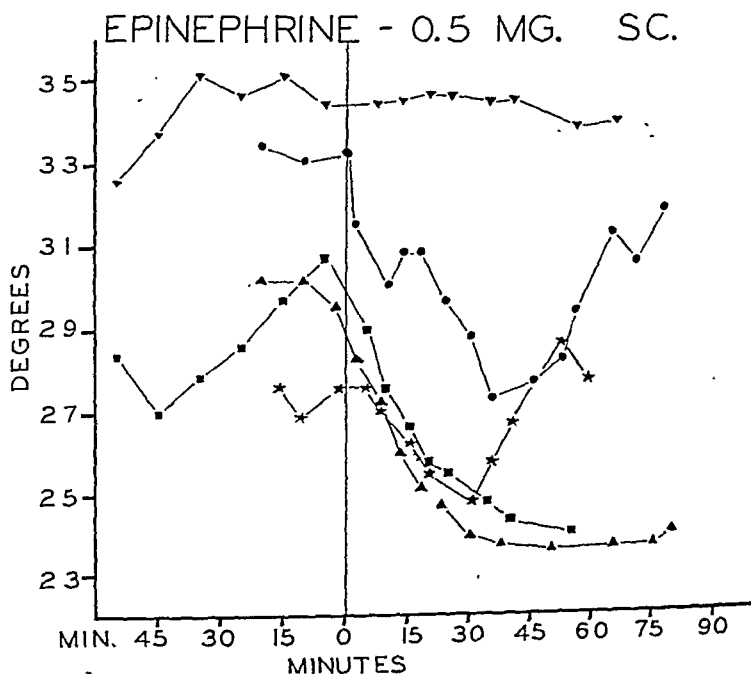
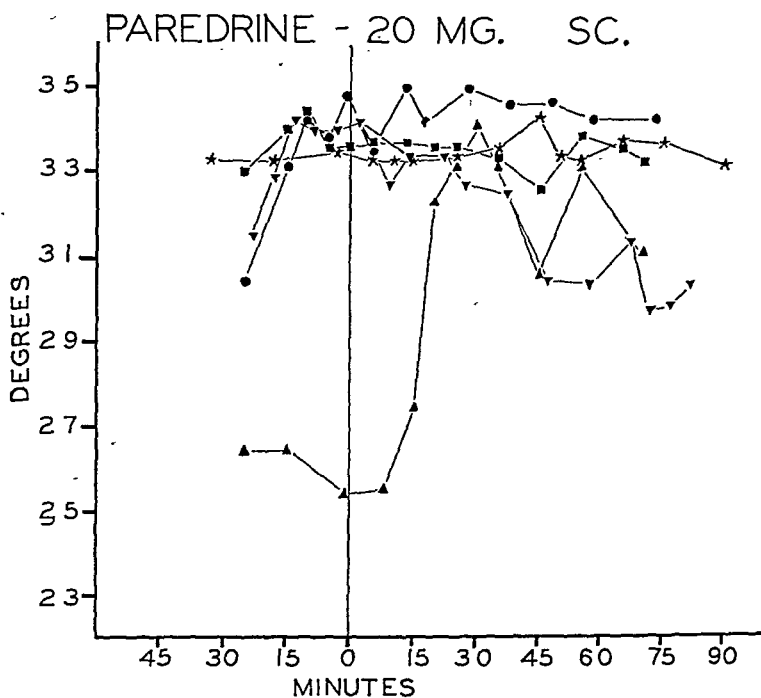


FIG. 4.—The comparative effects of paredrine and epinephrine upon the skin temperature. Effective doses of the two drugs were injected subcutaneously. From each group 5 cases were selected for presentation, those showing the greatest and the least responses being included.

evidence of a response to either 49 mg. by mouth or 20 mg. subcutaneously. Records of ileac contractions in the same individuals

BUERGER'S DISEASE. PERIARTERIAL SYMPATHECTOMY.

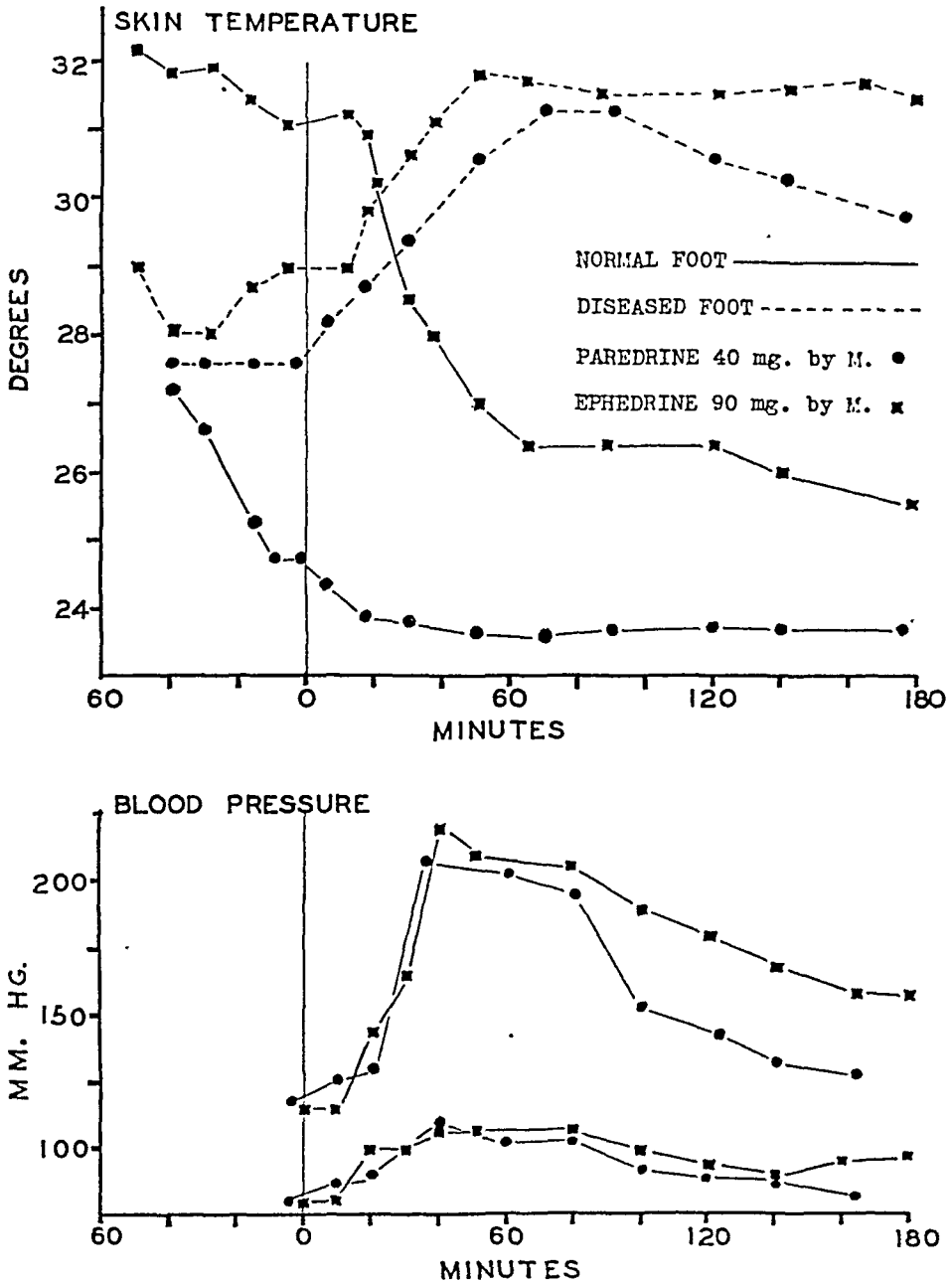


FIG. 5.—The effect of paredrine and ephedrine upon a case of Buerger's disease. The comparative effects of the two drugs upon the normal and upon the affected foot are shown. Though only the ephedrine caused a cooling of the normal foot, both drugs caused warming of the diseased foot coincident with the increased blood pressure. A bilateral periarterial sympathectomy had been performed upon this patient 6 weeks before these observations were made, but upon another case of Buerger's disease similarly operated upon, no such results were obtained.

showed, in one, after the oral dose no effect, in the other, after the subcutaneous injection a slight decrease in activity. Simultaneously with the taking of the balloon records in the subject receiving the subcutaneous injection, an opaque meal of barium sulphate was observed under the fluoroscope. Gastric activity remained normal, but a slight decrease in small intestinal activity was noted.

TABLE 2.—EFFECT OF PAREDRINE ON THE URINE FLOW.

Dose* in mg.	Mode of admin.	Age.	Rise in systolic B. P., mm. Hg.	Fluid intake per hour, cc.	Urine collections in cc.				Ratio.†	Pro- tein.
					1st hr.	2d hr.	3d hr.	4th hr.		
20	Mouth	50	24	100	40	75	80	115	10/17	0
20	Mouth	59	60	100	50	65	125	50	10/15	0
40	Mouth	30	54	100	40	140	140	125	10/15	0
40	Mouth	51	36	100	15	28	33	50	10/20	0
40	Mouth	21	10	100	33	235	75	60	10/5	0
40	Mouth	30	100	200	25	80	360	200	10/53	0
40	Mouth	26	52	200	75	225	650	260	10/30	+
40	Mouth	27	84	200	54	38	85	55	10/16	+
60	Mouth	26	62	200	52	140	470	320	10/41	0
60	Mouth	30	26	100	160	140	110	150	10/9	0
20	Hypo.	16	64	100	30	40	70	225	10/42	0
40	Hypo.	26	48	200	52	140	470	320	10/41	0
40	Hypo.	29	96	100	54	100	250	210	10/30	0

* Drug given after the second hour urine collection.

† Ratio of the average hourly output before and after the drug.

3. ON THE CENTRAL NERVOUS SYSTEM. In no subject receiving a dose insufficient to produce blood pressure elevation did central nervous system symptoms occur. With effective doses, palpitations, a sense of tightness across the lower chest and sweating occurred, but in none of them was a tremor of the fingers or a sense of apprehension apparent. Mild headache occasionally appeared, becoming very intense in the 3 subjects who showed marked reactions. It was impossible to know whether these effects were due directly to central nervous system stimulation by the drug or secondarily to the effects of the hypertension which it had produced.

4. ON THE RESPIRATORY SYSTEM. Aside from its local action on the nasal mucosa, the most important site of possible respiratory system effect was expected to be the bronchial musculature. As the normal subject provides little opportunity for detecting bronchial relaxation, asthmatics were studied during acute attacks. The drug was given in doses of 20 to 40 mg. by mouth and of 10 to 20 mg. subcutaneously to a few suitable patients during repeated attacks. While some slight relief of the attack was usually observed from 5 to 10 minutes after the time of administration, most of the attacks continued until epinephrine was injected. In no case did prompt relief of asthma occur following paredrine in a manner comparable to that seen after epinephrine.

B. Effects of Repeated Doses. Three bedfast patients, a boy of 16 years, and an adult, both with Pott's disease, and a second adult with chronic tuberculosis of the hip, were studied with regard to cumulative effects. After a week's observation of the pulse and blood pressure, a dose of 20 mg. of paredrine was given 3 times a day for a week. In none did a significant change in the blood pressure or the pulse occur. None complained of headache, insomnia, palpitations, loss of appetite, change in bowel habits or of pain.

C. Undesirable Reactions Following Systemic Administration. Following but 3 of the 574 doses of paredrine the effects of which we have observed, have definitely undesirable reactions occurred, and in each instance the dose was large. Two severe reactions occurred in group of 6 subjects who received 40 mg. of the drug subcutaneously, and 1 moderately severe reaction in the group of 14 who received the same dose by mouth.

Case Abstracts. CASE 1.—G. H., a white, male, medical student aged 23, in normal health, was given 40 mg. of paredrine subcutaneously. In 5 minutes the blood pressure had arisen from 112/50 to 132/60 with the appearance of mild palpitations. In 10 minutes the pressure had risen to 190/90 and a severe throbbing occipital pain had suddenly appeared. Extreme nausea followed as the blood pressure reached 200/90. Nitroglycerine (0.6 mg.) was given by mouth 25 minutes after the paredrine, with no apparent effect on the blood pressure or on the symptoms. Profuse sweating was constantly apparent and 15 minutes later vomiting ensued. A second 0.6 mg. dose of nitroglycerine was given $\frac{1}{2}$ hour later, again without effect on blood pressure or symptoms. The headache persisted in intense form for an hour, gradually subsiding as the blood pressure fell, but in modified form it remained throughout the next day, and appeared after the slightest exertion for 2 more days.

CASE 2.—M. S., a white woman aged 22, admitted because of migraine attacks recurring over a period of 4 years, was given 40 mg. of paredrine subcutaneously during a period of normal health. Within 5 minutes her blood pressure had risen from 108/76 to 140/86 and she began to complain of a pain in the right parietal region and of nausea. The pain then became diffuse and throbbing, rapidly increasing as the blood pressure rose to a peak of 170/90. At this time, 25 minutes after the paredrine injection, her pain was so intense that she was given an injection of acetyl β -methylcholine. Her blood pressure immediately fell to 104/50 with prompt abatement of the headache but with the usual drenching sweat. The pulse rose to 140. A dose of 0.4 mg. of atropine sulphate was injected subcutaneously 10 minutes later, and the blood pressure rose to 124/90, accompanied by a fall in pulse rate to 64. The pain then recurred with great intensity in the vertex, accompanied by nausea and vomiting, and persisted unabated until relieved by morphine. The subject described this reaction as being much worse than any of her migraine attacks.

CASE 3.—B. R., a white male aged 44, admitted to the hospital for the study of a chronic pain in the lumbar region, was given 40 mg. of paredrine by mouth. He developed a throbbing frontal headache 45 minutes later, by which time his blood pressure had risen from 98/68 to 184/120. Sweating, nausea and retching accompanied the headache, and all symptoms subsided together as the pressure fell. The headache disappeared 1 hour and 50 minutes after the paredrine had been given.

II. Local Administration. A. Ocular Effects.* In 22 instances the effects of a paredrine solution dropped into the conjunctival sac were observed (Table 3). The drug uniformly produced mydriasis, while in no instance was loss of accommodation observed. In no case was irritation felt or evidence of it seen. The intraocular tension was tested in 5 cases receiving solutions varying from 0.15 to 2%, but no increase in pressure was noted. The full mydriatic response usually appeared within 60 minutes, and the total duration of effect was about 6 hours. The mydriasis could be readily neutralized by miotic drugs.

TABLE 3.—EFFECT OF PAREDRIENE ON THE EYE.

(All solutions were administered by the instillation of 3 drops into the conjunctival sac.)

Concentration of paredrine, per cent.	Time intervals.			Degree of dilatation, mm.
	Beginning dilatation, min.	Maximal dilatation, min.	Duration of dilatation, hrs.	
0.1	0	0	0	0
0.1	0	0	0	0
0.15	30	60	6	3.0
0.15	0	0	0	0
0.15	15	75	6	3.0
0.15	0	0	0	0
0.15	50	50	..	0.5
0.15	50	50	..	0.5
0.15	0	0	0	0
0.15	0	0	0	0
0.15	30	70	..	1.5
0.25	10	20	6	1.5
0.25	20	50	6	3.5
0.25	30	50	6	2.0
0.25	30	50	6	2.5
0.25	20	50	6	2.0
0.25	25	60	6	4.0
0.5	15	45	7	4.0
1.0	15	50	7	4.0
2.0	13	120	7	5.0

B. Duration of Local Anesthesia. Two series of observations were made upon the power of paredrine to prolong procaine anesthesia following intradermal injection (Table 4). A solution of 0.2% paredrine was totally ineffective as compared to an epinephrine solution of 1:500 of that concentration. Instead of the zone of blanching produced by epinephrine at the site of injection, paredrine produced an erythematous area.

C. Action on the Nasal Mucosa. 1. NORMAL SUBJECTS. In 17 individuals, solutions of 0.25% were applied directly to the nasal mucosa. In no case did this fail to produce blanching and appreciable shrinking within 5 minutes. No irritation was complained of. The duration of this effect was from 2 to 3 hours.

* Our thanks are extended to Dr. W. E. Fry for his kind assistance in the making of these observations.

2. SUBJECTS WITH CONGESTION: In 22 patients with acute or chronic rhinitis it was determined that 0.25 to 1% was sufficient to produce shrinkage. Then to each patient was given a 1-week's supply and he was interviewed upon his return. All of 8 patients who received 1% paredrine had obtained unequivocal relief, while in the remaining 14 cases, variable results were secured.

TABLE 4.—THE EFFECT OF PAREDRIENE AND EPINEPHRINE ON THE DURATION OF PROCAINE LOCAL ANESTHESIA FOLLOWING INTRADERMAL INJECTIONS OF 0.1 CC.

Solution and concentration.	Per cent.	Duration of anesthesia.	
		Subject 1, min.	Subject 2, min.
Distilled water	10	20
Procaine	1.0	25	20
Paredrine	0.2	0	10
Epinephrine	0.002	20	0
<hr/>			
Procaine	1.0		
Epinephrine	0.001	85	75
Procaine	1.0		
Epinephrine	0.002	85	165
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Procaine	1.0		
Paredrine	0.01	30	10
Procaine	1.0		
Paredrine	0.05	15	20
Procaine	1.0		
Paredrine	0.1	25	25
Procaine	1.0		
Paredrine	0.2	25	15

3. A SUBJECTIVE COMPARISON WITH EPHEDRINE IN DISEASE CONDITIONS.* To each of 20 University students applying to the Student Health Department for relief of acute rhinitis or sinusitis, 3% ephedrine and either 1% or 3% paredrine in aqueous solution without a preservative were given. Those comparing the ephedrine with the 1% paredrine tended to favor the former as more effective, in spite of its local irritant quality. When 3% solutions of the two drugs were compared, a preponderance of opinion favored the paredrine as being equally effective and less irritant. The insolubility of paredrine in oil prohibited its use in this medium.

Discussion. The results of this study of the effect of paredrine on man, confirm in general the studies by Alles¹ and by Alles and Prinzmetal,² of the action of the drug on animals, and similarly their conclusion that it is a sympathomimetic amine. Like the other drugs of this type, it markedly increases the blood pressure, presumably due to its producing vasoconstriction, though if this be the case, it is not clear why no striking pallor, cooling of the skin, or oliguria such as was usually found by Starr³ to follow the adminis-

* Our thanks are due to Dr. H. D. Lees and to his staff in the Student Health Department of the University of Pennsylvania, for granting us the facilities for this study, and for invaluable coöperation in carrying it out.

tration of epinephrine and ephedrine, was detected, or furthermore, why the drug fails to prolong local anesthesia in the skin, and why when injected intradermally it sometimes produces a local flush. A point perhaps of practical interest, though one not specific for paredrine, was its effect in a case of Buerger's disease in increasing the local temperature of the diseased part. In the observed individual, the leg vessel whether from increased rigidity, or less probably from partial ablation of the vasoconstrictor nerve supply, appeared to react as an inert tube by conducting a greater volume flow in response to a greater head of pressure. The slowing of the pulse following paredrine administration is doubtless a reflex through the depressor mechanisms, for the extrasystoles and the instances of coupled beats observed suggest, if anything, an increased irritability of the heart.

Gastro-intestinal actions, if any are produced by this drug, are probably of no practical significance.

The central nervous system may be stimulated, but little has been observed by us that could not be attributed to the rise in blood pressure *per se* since Schmidt⁵ has shown that drugs raising the blood pressure increase the blood flow in the brain. No residual tremor or insomnia has been seen in subjects taking repeated doses, and residual headache after the fall in blood pressure has occurred but once in our subjects.

In the relief of asthmatic attacks we have been unsuccessful with doses which we felt at liberty to use.

In the eye it appears to be a harmless, but effective, mydriatic of rather evanescent action, and perhaps advantageous for use in temporarily dilating the pupil.

Upon the nasal mucosa, paredrine has an action like ephedrine, and probably distinguishable from it only by being somewhat less irritant in water solution. If in the course of time it should prove to be free from a central nervous system stimulating activity, it might find a place as an ephedrine substitute, though lack of solubility in oil is a point against it in this regard.

It may be said then, that in the light of our experience with the action of paredrine upon human subjects, it may be defined as a sympathomimetic amine of considerable potency and fair reliability, whether given by mouth or subcutaneously, exhibiting its most definite effect by raising the blood pressure, and possessing potentialities for an extreme and unexpected vigor of action that suggest more an idiosyncrasy than a slight increase of susceptibility on the part of the subject for the drug.

Summary. 1. Paredrine is a drug related in chemical composition to epinephrine and ephedrine.

2. In raising the blood pressure it is about one-fiftieth as potent as epinephrine if given subcutaneously, and is about twice as potent as ephedrine when given by mouth.

3. Its chief clinical actions are to raise the blood pressure, to dilate the pupil and to constrict the nasal mucosa.

4. It occasionally produces exaggerated reactions suggesting an idiosyncrasy rather than an overdosage.

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OBSERVATIONS ON CORAMINE.

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THE first published reference to the drug, Coramine, appeared in a paper by Lagier,¹¹ in which, under the name nicotinic acid diethylamide, its pharmacologic properties were discussed. Two years later, Faust⁶ suggested the more properly descriptive name, pyridine-beta-carboxydiethylamide, and briefly reviewed the facts regarding its synthesis and physiologic actions. Using a 25% aqueous solution under the trade name, Coramine, Thannhauser and Fritzel¹⁴ concluded that the new drug was of definite value in the treatment of collapse and of cardiac decompensation. The interest aroused by Coramine since Lagier's report has been marked; almost 1400 publications dealing with it have made their appearance. Obviously, it would be impossible adequately to review these reports in the limits of a single paper; partly because of this and partly because of the excellent reviews recently published by Wood¹⁷ and Daly,³ only those papers bearing directly on the problem which engaged my interest will be discussed in any detail in the present communication.

That Coramine is a powerful respiratory stimulant has been definitely established; the action being directly on the medullary center or through the carotid sinus. The direct application of this respiratory action has been made successfully in many forms of respiratory depression: as in the course of certain acute infectious diseases or in poisoning by carbon monoxide, anesthetic agents, or by overdosage with various hypnotic drugs. The demonstration of a direct action of Coramine on the circulation offers difficulties in intact animals and human beings. There is, first, the complicating factor introduced by the well-recognized respiratory stimulation from Coramine; the deeper and more forceful respirations improving flow of blood to the heart. Then, too, various adjustments and alterations in the circulatory system may, at times, be compensa-

tory in nature, and at others be so combined as to render positive explanation impossible. Experiments with the isolated heart are open to the objection that conditions with it are so utterly artificial as to fail to give a correct picture of the behavior of this organ in the intact animal.

The results of experiments carried out by different investigators with the object of ascertaining the nature of the Coramine action on the circulation have not been in complete harmony, as might be anticipated from the brief outline of the difficulties in the way of a study of such a nature. The earlier investigators, Lagier,¹¹ Faust,⁶ Uhlmann,¹⁵ Asher,¹ and Burgi and Gordonoff,² concluded that Coramine was a stimulant to the circulation, acting on the myocardium or by vasoconstriction. Leyko,¹² employing the Starling heart-lung preparation from the cat, described an increase in diastolic excursions of the heart and an increase in coronary flow following administration of Coramine. This increase in coronary flow was also observed by Greene;⁹ and Mezey,¹³ noting a similar effect on the coronary vessels, reported an increase in the diastolic excursions of the heart in the Starling preparation when Coramine was injected.

Numerous clinical observations suggest circulatory improvement from Carmine medication.^{3, 8, 10, 16, 17} Especially worthy of note were the observations by Guth,¹⁰ showing that the administration of Coramine was followed by a definite increase in the rate of blood flow. In this country, Wood¹⁷ has used Coramine chiefly for its action on the respiration; but he offers evidence to indicate that under its influence the depressed circulation, also, is stimulated by the drug. Daly,³ too, finds that Coramine is of distinct value, not only as a respiratory stimulant but also because of its favorable action on the myocardium. Gilmore⁸ reports excellent results following Coramine administration to patients with the so-called "neuro-circulatory asthenia," a condition which this author regards as a definite pathologic entity and not merely a manifestation of a neurotic constitution. In a recent excellent paper dealing with acute coronary thrombosis, Winslow¹⁶ states that both respiratory and circulatory stimulation may be effectively produced by Coramine; expressing the opinion that it is "a rapidly acting, non-toxic heart stimulant, as well as a coronary dilator."

Studies of the electrocardiographic changes induced by Coramine are few. Frommel⁷ states that the electrocardiograms of frogs and toads show a slowing of the heart rate and a shortened *P-R* interval under its influence. In guinea pigs and rabbits, on the contrary, there occurs a tachycardia, apparently from an action on the sinoauricular node. The *P-R* interval is shortened in the heart of these warm-blooded animals also; but slowing of the heart and *A-B* block may occur in the agonal stage after administration of fatal doses of the drug. The previous administration of atropine does not modify

the effect of Coramine on the batrachian heart; but section of vagi and sympathetic in the guinea-pig lessened the response to Coramine subsequently administered. Eisner⁴ compared the effects of Coramine with those of digitalis and camphor in a small series of patients, and concluded that Coramine had no effect on conductivity, differing thus from digitalis.

The present investigation was undertaken in the hope of shedding additional light on the circulatory action of Coramine, chiefly by electrocardiographic studies, but also by other observations which yielded results at times that were of interest. Eleven patients were observed over varying periods of time: 5, with no organic lesions of the heart, as controls; 6 with various types of heart disease. In all instances, a control electrocardiogram was taken before institution of Coramine administration, and later tracings were made at frequent intervals during the period of observation. Coramine was given orally in fruit juices; the oral administration being supplemented in certain instances by intramuscular or intravenous injection of the ampule solution. All other medication, save the Coramine, was discontinued during the study, except when the contrary is noted. The essential data obtained in this study are given in the following abridged case histories.

Case Abstracts. CASE 1.—A female hospital librarian, aged 55, weight 161 pounds. Examination is essentially negative, except that heart is slightly enlarged and blood pressure low, 100/78. B. M. R. varied from -1 to -25. On March 26, 1936, control electrocardiogram showed left axis deviation, sinus arrhythmia; *P-R* interval, 0.18 second; *Q R S*, 0.04 second. On this day, Coramine, 20 minims twice daily by mouth, was commenced.

On March 30, 1936, after 4 days' medication with Coramine, the patient volunteered the statement that she was feeling better. Her blood pressure was 115/70 and heart sounds were more distinct. Electrocardiogram: sinus rhythm; *P-R* interval, 0.16 second; *Q R S*, 0.04 second.

Repeated electrocardiograms were taken between March 30 and May 10, 1936. At this latter date, patient felt greatly improved; her blood pressure was 130/80, and her weight 170 pounds. Electrocardiogram showed left axis deviation; sinus rhythm; *P-R* interval, 0.16 second; *Q R S*, 0.06 second. The ventricular complexes showed evidence of increased electrical voltages and the *T* waves in Leads 1 and 2 were slightly reduced.

Comment. Coramine was given by mouth, 20 minims morning and evening, over a period of 47 days; a total of 1880 minims (nearly 4 ounces) being taken. This patient, belonging to the group of neurocirculatory asthenia, was clinically improved during the period of Coramine administration. There was a decided absence of complaints, a continuous sense of well-being; the hypotension, which usually ranged from 100 to 110 systolic and seemed to be such a disabling factor, was elevated to 130, with a pulse pressure ranging from 40 to 50 mm. Given over a period of 7 weeks by mouth, Coramine produced no untoward physiologic effects such as nausea, vomiting, diarrhea or anorexia; on the contrary, in this particular

instance, appetite was improved and the patient gained 9 pounds. The urine remained normal during the entire period. Cardiographically, no evidence of toxic changes in any of the components of the cardiac cycle could be demonstrated. The earliest graphic changes appeared to be an increase in the voltage of the main ventricular complexes of all leads, which changes remain consistently. Changes in the size and shape of the *T* wave of Leads 1 and 2 occurred, essentially directed toward a lowering of the voltages slightly, and a tendency of these waves to become diphasic. (The phenomenon of electrical alternation which was present at the onset of this observation was more clearly emphasized under the administration of Coramine.)

CASE 2.—A male laborer, aged 41, weight 107 pounds. Examination was negative, save for a heart rather small in size. On March 21, 1936, control electrocardiogram showed *P-R* interval, 0.18 second; *Q R S*, 0.04 second. Coramine, 30 minims twice daily was started.

Two days later, patient reported that he felt better. The electrocardiogram on this date showed no material alteration from control, except slight increase in the size of the main ventricular complexes in Lead 2, and an increase of from 2 to 3 mm. in Lead 3. The heart sounds were definitely louder than at the time of the first observation. On April 6, electrocardiogram showed sinus rhythm; *P-R* interval, 0.18 second; *Q R S*, 0.05 second; and *P I* isoelectric. The *T* waves were larger in all leads.

Comment. Coramine was administered by mouth over a period of 35 days, the total quantity taken being 140 cc., with no untoward effects. No toxic changes could be demonstrated clinically, or graphically in serial electrocardiograms taken over this period. The most pronounced and consistent changes were an elevation of the voltage of the main ventricular complexes in all the leads, but most marked in Lead 2, lesser fleeting changes occurred in the *T* waves. Clinically, this patient remained in a state of euphoria, with good appetite, and volunteered the information that he was able to carry on his work with greater efficiency and less fatigue.

CASE 3.—A male laborer, aged 40, weight 150 pounds. Examination negative, except for blood pressure of 100/65. On March 24, 1936, control electrocardiogram showed sinus rhythm; *P-R* interval, 0.16 second; *Q R S*, 0.04 second. The administration of Coramine, 30 minims twice daily, was started. March 26, patient reported no change. Electrocardiogram showed a *P-R* interval of 0.18 second and *Q R S* of 0.08 second, with increase in the amplitude of all the components. The final electrocardiogram, June 1, 1936, showed sinus rhythm; *P-R* interval of 0.16 second; *Q R S*, 0.08 second.

Comment. No significant changes were noted in blood pressure reading, pulse rate, heart sounds or urinalyses. Graphically the earliest change, noticed following the administration of Coramine, was an increase in the voltage of all the main ventricular complexes, which remained consistently throughout the investigation. Lesser changes in the *T* wave were variable.

CASE 4.—A female laundry worker, aged 26, weight 127 pounds. Examination revealed, as the only significant feature, a very active carotid sinus reflex.

On March 26, 1936, electrocardiogram showed sinus rhythm; $P-R$ interval, 0.16 to 0.18 second and QRS , 0.08 second. Coramine, 20 minims twice daily, was started.

April 2, the patient was euphoric. Electrocardiogram showed sinus rhythm; $P-R$ interval, 0.16 second; QRS , 0.06 second. There was a small U wave in Leads 1 and 2. Lead 1 showed a nodal or ventricular premature beat in the course of normal sinus rhythm; $T3$ isoelectric and tending to positivity. Ventricular complexes in Leads 1 and 3 showed increased amplitude.

Comment. This control case was available for only a short period of study, subsequent efforts to gain her coöperation being of no avail because she said she felt so well. A total of 24 cc. of Coramine orally was administered to this patient with no untoward physiologic or toxic effects. This patient was subject to fainting or syncopal attacks as a result of a bradycardia from an unusually high vagal influence. This was very beautifully demonstrated in the electrocardiogram by using only gentle pressure over the carotid sinus, as on one occasion the heart rate dropped to 20 on moderate pressure, and she represented such a sensitive mechanism I was afraid to manipulate too vigorously for fear of producing ventricular standstill. During this period of Coramine administration she experienced no faintness or syncope. The heart remained about 80 and the patient felt well. The earliest graphic change was an increase in the voltage of the main ventricular complexes, this change remaining consistently until observation ceased.

CASE 5.—A tailor, aged 44. Physical examination negative. On April 10, 1936, control electrocardiogram showed left axis deviation; sinus rhythm; $P-R$ interval, 0.18 second; QRS , 0.08 second. Coramine, 20 minims three times daily, was started. April 22, after a total dosage of 720 minims of Coramine, patient showed a gain of 6 pounds and reported that he was definitely more energetic and able to carry on his work with less fatigue. Electrocardiogram on this date showed left axis deviation; $P-R$ interval of 0.2 second; QRS , 0.08 second; enormously large $T1$, 10 mm. in height; $T2$, 7 mm. in height; and $T3$ inverted.

Comment. These changes were particularly present in Leads 1 and 2. Taken over a period of 12 days the patient showed no untoward physiologic effects. He reported a state of well-being at all times, an increased efficiency in performing his work and a lesser consciousness of fatigue.

The cardiac and circulatory efficiency appeared to be increased by the Coramine administered. Apparently improvement in the stroke output and the minute volume output definitely increased the work capacity of the heart, thus bringing about an enhanced circulatory efficiency.

CASE 6.—A male piano worker, aged 60, with a history of a chancre 30 years ago, and only local treatment. Substernal pain on exertion for the past 5 years and attacks of nocturnal dyspnea. His systolic blood pressure was stated to be 238 mm. in January, 1934, and a 4+ Wassermann reaction was reported at this time. Active antiluetic treatment was carried out for 2 years, but his condition became steadily worse, so that he was unable to walk without development of substernal pain.

April 12, 1936, examination revealed a well-nourished man with a blood pressure of 180/0. Eye grounds showed narrow, tortuous vessels. Left border of heart well outside nipple line. Loud diastolic murmurs heard in second right interspace and at the base to the left of the sternum. Corrigan pulse, tracheal tug, pulsating cervical vessels, and other signs of aortic regurgitation were present. Fluoroscopy in the *A-P* view showed a marked rounding and elongation of the heart and elongation of the aorta, with accentuated knob. The descending aorta was enlarged and probably aneurysmal. Slight enlargement of the liver. The diagnosis was luetic aortitis, with aortic regurgitation, and aneurysm. April 13, 1936, control electrocardiogram showed sinus rhythm; *P-R* interval, 0.2 second; *Q R S*, 0.08 second. The *Q R S* was aberrant; *T2* and *T3* were negative and cove plane; *P2* broad and bifid. Coramine, 30 minims twice daily, was started April 15, electrocardiogram unchanged, save for some increase in the amplitude of the main ventricular complexes. May 11, patient reported that he was definitely better and that he had walked up a steep hill without dyspnea or substernal pain. Blood pressure was 158/0. May 18, patient volunteered the information that he had not felt so well for the past 2 years. He was able to continue his work as a piano tuner with no discomfort. The electrocardiogram on this date showed a great increase in the voltage of the main ventricular complexes in Lead 2.

Twice to three times weekly, 5.5 cc. of Coramine were injected intramuscularly in addition to the regularly administered oral medication. May 20, patient was not complaining, but on auscultation of the heart sounds, premature beats within the regular sinus rhythm could be detected at every eighth, or at times, every fourth beat. The electrocardiogram showed a *P-R* interval of 0.2 to 0.26 second and, in Lead 2, coupled rhythm at intervals of 4 to 8 beats, and the occurrence of premature auricular beats in the Lead 3, the question arose as to whether these changes were signs of an early toxic action of Coramine. Since the man's condition was good, it seemed permissible to continue Coramine medication under careful observation. On May 25 the patient complained that his heart had been acting queerly, but the electrocardiogram on this date showed no arrhythmia. Oral and intramuscular administration of Coramine was continued. June 5, after a total of more than 8 ounces of Coramine, the electrocardiogram was negative, save for a *P-R* interval of 0.2 to 0.22 second. The patient continued to feel improved.

Comment. In this patient, with severe organic cardiac disease, the continuous administration of Coramine, orally and by intramuscular injection, until a total of over 8 ounces was given, resulted in an apparent improvement in the man's condition and no signs of toxic action.

CASE 7.—A housewife, aged 30, weight 135 pounds, gave a history of rheumatic fever, recurring annually or semi-annually. Has recently noted dyspnea on exertion. Physical examination revealed a loud, blowing systolic murmur in the mitral region and heart enlarged considerably to the left. Control electrocardiogram showed sinus rhythm; *P-R* interval, 0.14 to 0.16 second; *Q R S*, 0.06 second; large *T* waves, and slight aberration of

Q R S1. Coramine, 30 minims twice daily by mouth, started April 15; in addition, the patient was given 1.5 cc. of Coramine intramuscularly twice weekly. May 8 steady improvement reported, but no electrocardiographic changes of note had occurred. Today she complained of palpitation. Electrocardiogram showed no change from the control taken April 15, except *P-R* interval was 0.18 second and the amplitude of the main ventricular curves was slightly increased. May 18, blood pressure 110/80. Electrocardiogram showed sinus rhythm; *P-R* interval, 0.18 second; *Q R S*, 0.06 second; slight decrease in the voltage in Lead 3.

Comment. Observation of this case covered a period of 33 days, during which time a total of 140 cc. of Coramine was administered by mouth and hypodermatically. The patient showed no untoward physiologic or toxic effects. Clinically, the patient showed a greater degree of efficiency in performing her duties and an absence of breathlessness. The earliest graphic changes demonstrable were increases in the voltage of all the main ventricular complexes, which effect seemed to be consistently sustained.

CASE 8.—A seamstress, aged 60, weight 100 pounds. Right breast had been amputated because of carcinoma, but metastasis had occurred and patient was admitted to the hospital suffering from generalized carcinomatosis. On April 17 she became delirious and developed signs of pulmonary edema. When seen, her pulse varied from 150 to 200 to the minute and was thready in character. Heart sounds feeble and fetal in character. Patient seemed *in extremis*. A liter of 5% glucose in physiologic saline was given by rectum. At 4 P.M. patient's condition seemed extremely critical and death was expected momentarily. An electrocardiogram taken at this time showed extreme tachycardia, and the complexes associated with exaggerated heart hurry. Coramine, 3 cc., injected intramuscularly and, at 5.30 P.M., an additional 5 cc. injected. At 10 P.M. pulse rate was steady at 150 to the minute and of definitely better quality. Respiration was less labored and stertorous.

April 18, 10 A.M., patient was given 5 cc. Coramine intramuscularly. She was now fully conscious and rational; pulse, 140 to the minute, of good quality. April 22 a total of 39 cc. of Coramine had been injected and the patient had a most dramatic improvement. At noon on this day, however, she suddenly developed a high temperature and signs of hypostatic pneumonia, and, despite all therapeutic measures, succumbed during the evening.

Comment. This case was selected to show the effect of Coramine on the dying heart in a case of terminal carcinomatosis. So far as is known, no previous history or findings of organic cardiac alterations existed. When the control electrocardiogram was taken, the patient was almost moribund. Serial tracings were taken at intervals from the onset of Coramine administration, and, if these are followed, it can be seen how the early sinus tachycardia with a rate of 160 and showing the bizarre complexes associated with an extreme heart hurry, changed to a more normal appearance with the individual waves assuming a more distinct form and shape, and slowing of the rate to 130. Clinically, the patient began to improve within a few hours after the initial dose, coming out of coma, asking for nourishment and being able to sit up. Pulmonary edema was con-

siderably relieved, the respiratory rate lowered and not labored. The patient continued to hold her own for 5 days. On the sixth day she developed a high temperature, severe cough with hypostatic congestion and died within 12 hours with a picture of pneumonia.

CASE 9.—A male laborer, aged 39, with history of old luetic infection and a 4+ Wassermann test. Five months ago, began to experience substernal pain, breathlessness, and a feeling of abdominal distention. Physical examination revealed a small, fairly well-nourished individual with marked pulsation of cervical vessels. Tracheal tug and water-hammer pulse present. Loud murmurs heard over entire chest, with a rumbling, diastolic one in second right interspace. Heart was enormously enlarged; transversely occupying three-fifths of the thoracic cage. On fluoroscopy, violent pulsations, characteristic of regurgitation, were seen in aortic arch.

April 22 control electrocardiogram showed sinus rhythm, rate 85; left axis deviation; *P-R* interval, 0.16 second; *Q R S*, 0.06 second; *ST*, 0.24 second; *T* waves negative in all leads; muscle damage. Coramine, 30 minims morning and evening, commenced. April 27 patient reported that he was feeling better. By intravenous injection, 5.5 cc. of Coramine was administered. Immediately after completion of the injection he became deathly pale and broke out in profuse sweat. Râles were audible in the pulmonary bases, suggesting edema of the lungs. Pulse slowed to between 30 and 40 to the minute and became irregular; the heart sounds were only faintly audible. The patient was placed in the recumbent position and a tablespoonful of rum given by mouth. Within 5 minutes his color improved and pulse had returned to its original rate, the patient complaining only of "light-headedness." An electrocardiogram taken 10 minutes later showed sinus rhythm; left axis deviation; rate, 80; *P-R* interval, 0.16 second; *Q R S*, 0.06 second; *S-T*, 0.26 second; *T* waves unchanged from control, also no essential change from control.

May 8 patient reported that he could walk better without discomfort. Dyspnea was now very slight. June 1 patient commenced light work. His condition seemed vastly improved. Electrocardiogram showed no material change, the main ventricular complexes being of exceedingly high voltage. June 12 a total of over 9 ounces of Coramine having been given orally and intramuscularly over a period of 53 days, the patient states that his ability to work is much greater.

Comment. Clinically, this patient appeared to be improved by the above therapy; from a state of inefficiency he continued to improve gradually until he was able to assume light work. At no time did he show, after May 27, 1936, any physiologic or untoward toxic manifestation. Graphically, the earliest change noted was an increase in the voltage of all the main ventricular complexes which was sustained.

CASE 10.—A male WPA worker, aged 58, complained of edema of ankles since early in 1935, and dyspnea on exertion since the first of 1936. April 22, 1936, patient's heart was found considerably enlarged to the right, and systolic murmurs were present at apex and over aortic area. Control electrocardiogram showed no axis deviation; *P-R* interval, 0.2 second; *Q R S*, 0.08 second; *S-T*, 0.28 second; low voltages in Lead 1 with an aberrant main ventricular complex. *T2* and *T3* negative. Coramine, 5 cc., given intramuscularly, and 30 minims twice daily ordered. May 11 patient had been reporting at frequent intervals and an apparent improvement, without alteration in the electrocardiograms, had been observed. Today,

however, although he had no complaint, the first break in rhythm was noted, a run of quintageminae occurring, suggesting the development of a new pace-maker in the A-V node, its influence vying with that of the sino-auricular node. May 20 electrocardiogram showed sinus rhythm, with an occasional run of premature beats. This appearance suggested a possible toxic action of the drug, but oral medication, 30 minims twice daily, continued. May 25, patient showed definite evidence of failing compensation; dyspnea, cyanosis, legs edematous to knees, and edge of liver two fingers' breadth below costal margin. Electrocardiogram showed sinus rhythm; a general lowering of voltage; flattening of T2 and inversion of T3. Coramine was discontinued. June 1 patient seemed worse; all signs of congestive failure had increased since last observation. June 3 patient's condition remaining unimproved, he was given salyrgan, 2 cc. intramuscularly. June 8 profuse diuresis had taken place, with loss in weight of 4½ pounds. Patient felt decidedly better; edema had almost disappeared; color improved and respiration practically normal.

Comment. This patient was observed over a period of 28 days, during which time he received a total of 147.5 cc. of Coramine both by mouth and hypodermatically. No toxic manifestations were noted until the patient had taken the drug for 16 days and 84 cc. were administered. At this time the electrocardiogram showed a cessation of normal sinus rhythm for the first time. Following this, more or less frequent premature ventricular and auricular beats appeared until, on the 28th day, the patient showed a very definite bigeminal rhythm and increasing signs of failure. He appeared so ill that all medication was discontinued and an attempt to restore compensation was made. Mercurials only were sufficient to restore broken compensation and bigeminal rhythm disappeared. It is, of course, impossible to say whether Coramine medication was in any way responsible for the failure in compensation or whether this occurred in spite of the Coramine. It is to be recalled that this patient showed marked heart muscle change and that he continued up and around while taking Coramine.

CASE 11.—A married female, aged 45, noted dyspnea on exertion 18 months ago. Six months later she received digitalis with definite subjective relief. May 6, 1936, examination revealed blood pressure of 150/100 and absolutely irregular pulse. By fluoroscopy, a heart occupying three-fifths the transverse diameter of the chest was seen. The diagnosis was rheumatic endocarditis with valvular disease and auricular fibrillation. The control electrocardiogram showed auricular fibrillation, with a ventricular rate of 150 to 160. Whole leaf digitalis tablets, 1½ grains 3 times daily, and Coramine, 30 minims twice daily, were ordered. May 20 patient, who had been reporting twice or three times weekly, was remarkably improved. She stated that she had been able to do a fairly hard day's work without discomfort. May 25 patient was in excellent spirits; blood pressure, 140/70; pulse rate, 58; ventricular rate, 63. The electrocardiogram showed a depression of the S-T segments, characteristic of digitalis overdosage; consequently the latter drug was reduced to 1½ grains daily. May 27 ventricular rate and pulse rate coincided; 52 to the minute. Digitalis reduced to 1½ grains every other day. June 15 ventricular rate 56, with no pulse deficit. A total of slightly over 5 ounces of Coramine were administered orally and intramuscularly over a period of 40 days.

Comment. This case of chronic rheumatic mitral disease with permanent auricular fibrillation in congestive failure was observed over a period of 40 days, receiving a total of 167 cc. of Coramine both by mouth and hypodermatically, showed no untoward physiologic or toxic effects. Clinically, this patient was out of congestive failure in 48 hours and restored to a working efficiency basis in 4 days, since which time she had withdrawn her digitalis for a few days while constantly taking Coramine in small doses. Coramine seemed to have kept this patient in a euphoric state, with a marked improvement in myocardial reserve.

Discussion.—The effect of Coramine on the blood pressure of the patients in this series was not striking or constant, but there was a tendency toward elevation of both systolic and diastolic levels. In Case 1, with a preëxisting hypotension, there was a very definite increase in the pressure and, accompanying this, a marked improvement in the patient's subjective sensations. We should not lose sight of the fact, however, that the absence of blood pressure change does not eliminate the possibility of an effect on the circulation; vascular relaxation may accompany increased cardiac output, with the result that blood flow is increased without rise in systolic pressure, or, indeed, even with a decline in the pressure. Case 9 manifested, after intravenous injection of 5.5 cc. of the ampule solution of Coramine, symptoms suggestive of a transient, rather alarming vascular relaxation. We were dealing here with an individual whose cardiovascular system had been severely damaged by luetic disease and in whom, consequently, the adjustive mechanisms functioned poorly. However, even in this case, recover occurred so promptly that the experience served to strengthen my belief in the low toxicity of Coramine, a belief seemingly justified by the entire absence of untoward symptoms in patients with normal hearts after very large amounts of Coramine; some of the foreign observers having injected in a single dose as much as 15 cc. of the ampule solution.

In only 2 other cases did symptoms suggesting possible toxic action of Coramine occur. One of these, Case 6, was an elderly man with luetic disease of long duration and advanced degenerative changes in heart and blood vessels. During the period of observation, he continued up and around, at first showing distinct improvement under Coramine medication. After 37 days, having received a total of 193 cc. of Coramine orally and intramuscularly, premature beats were detected and there was slight increase in the *P-R* interval. The findings might be interpreted as indicative of early toxic action of Coramine; however, continued administration of the drug was followed by a disappearance of the premature beats and improvement in general condition. Observation was discontinued after 54 days and a total dosage of 290 cc. of Coramine.

In Case 10, also, there was evidence of advanced organic change in heart and arteries, harmonizing with the distressing symptoms

manifested prior to commencing Coramine administration. The electrocardiogram taken 27 days after institution of Coramine therapy suggested the possibility of a toxic action from the drug, and, 5 days later, the patient's condition was definitely worse, with clear-cut congestive failure. That the undesirable results seen here were due to Coramine is by no means established. With a badly damaged heart, the patient continued up and around, and the physical exertion to which he was subjected may well have been the precipitating factor in bringing on his break. Certainly, no improvement occurred on discontinuance of Coramine until after diuresis had been effected by injection of Salyrgan.

That Coramine acts directly on the heart is indicated by the increased voltages seen in the electrocardiogram after its administration. In Case 8, the dramatic recovery of a patient almost moribund is impressive evidence as to the efficacy of Coramine under certain conditions. Here, with large doses, there was continuing improvement until hypostatic pneumonia developed on the 6th day. As suggested by Frommel,⁷ Coramine may affect the heart through its extrinsic nerve supply. Stimulation of the sympathetic would not only cause increase in the force and frequency of the contractions, but would also tend to bring about the coronary dilation which has been demonstrated to take place.^{9, 12} As further indicative of the favorable influence of Coramine, the course of events in Case 11 may be briefly recalled. This patient, with auricular fibrillation, a ventricular rate of 150, and congestive failure, showed rapid improvement after receiving a total of 9 grains of powdered digitalis leaf and 12 cc. of Coramine orally during 48 hours. In spite of the fact that she remained active, at times doing rather strenuous housework, she continued to improve and, at the end of 40 days, showed no pulse deficit nor other indications of cardiac incompetence. The digitalis was given in doses of $1\frac{1}{2}$ grains t. i. d. for 7 days and then reduced to $1\frac{1}{2}$ daily, and, finally to $\frac{3}{4}$ grain daily. The total dosage for Coramine during the 40-day period was 167 cc., partly by mouth and partly by intramuscular injection. This apparent synergism between Coramine and digitalis is in harmony with the experimental results reported by Fahrenkamp and Nocke,⁵ which establish the fact that administration of Coramine sensitizes the heart to the subsequent action of digitalis, so that effects from the latter drug are obtainable from concentrations which, alone, would have been ineffective.

Conclusions. The effects of Coramine were observed in a series of 10 ambulatory and 1 bedridden patient following varying periods of administration in the different cases. Five of the patients showed no evidence of organic cardiovascular disease and were designated as controls; 5 showed distinct organic changes in the heart; and 1 suffered from acute circulatory collapse associated with toxemia

from generalized carcinomatosis. From the experience gained in these patients, the following conclusions seem justifiable.

1. The margin of safety for Coramine is wide, as regards either the single dose or use over prolonged periods of time.

2. Electrocardiographically, the drug causes an increase in voltage for all the main ventricular complexes; an increase that is generally well sustained. There occur, at times, lesser and more variable changes in other components, such as the *T* wave and *P-R* interval. A few observations suggest that the *A-V* conductivity may be slightly depressed in patients with badly damaged myocardia.

3. Subjective and objective changes pointed to increased myocardial efficiency after sufficient dosage with Coramine. This improvement may be due to (a) an action on the extrinsic cardiac nerves; or (b) to a direct action on the heart muscle; or (c) to an increase in coronary flow.

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THE VARIABILITY OF THE VITAL CAPACITY OF THE LUNGS IN YOUTH.

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IN 1796, an instrument called a "mercurial air holder and breathing machine" was devised by Clayfield^{1b} by means of which the breathing capacity could be measured. Fifty years later, Hutchinson⁴ improved upon Clayfield's machine, and studied the breathing capacity of many individuals. He called his new instrument the "spirometer," changed the term breathing capacity to "vital capacity," which he defined as "the amount of air which can be exhaled after the deepest possible inspiration," and devised standards for predicting from the height of the subject what his vital

capacity should be. Since a diminution of the vital capacity was known to occur as a result of certain diseases of the heart, lungs and adjoining structures, it was hoped that by means of the spirometer these diseases might quickly and accurately be detected. Unfortunately, this hope was not realized and the spirometer did not find its way into the office of the general practitioner. This is not to be wondered at if we consider the analogy between vital capacity and weight. How many practitioners' offices would be equipped with scales if the only use made of the weight was to compare it to a table to see whether the patient's weight was above or below the average for his height and age? From a diagnostic standpoint an actually observed loss of 10 pounds would be regarded by any practitioner of experience, as more important than the fact that an individual was 20 pounds below the average for his height. The same is true of the vital capacity as has been shown by one of us (J. H. A.).^{1a}

In taking the vital capacity of the same student in each successive year as part of our annual physical examination, we have been struck by the fact that while in many cases little or no variation occurs in the successive vital capacity determinations, in others we see considerable variation. Obviously a fall in the vital capacity would mean less in a student whose vital capacity was known to be variable, than in one who had maintained the same reading for several successive years, or whose vital capacity readings showed a steady gain. The present paper aims to present a study of the frequency and size of these fluctuations in order that the limitations or dependability of the test may be better understood.

Method. The study is based upon yearly vital capacity readings in 100 males and 100 females of college age. The same spirometers were used throughout, being tested from time to time for accuracy. At least 3, and frequently more, readings were made in each case by assistants trained and supervised by one of us (J. H. A.). Students in whom there existed any suspicion of disease which might affect the vital capacity were omitted from consideration.

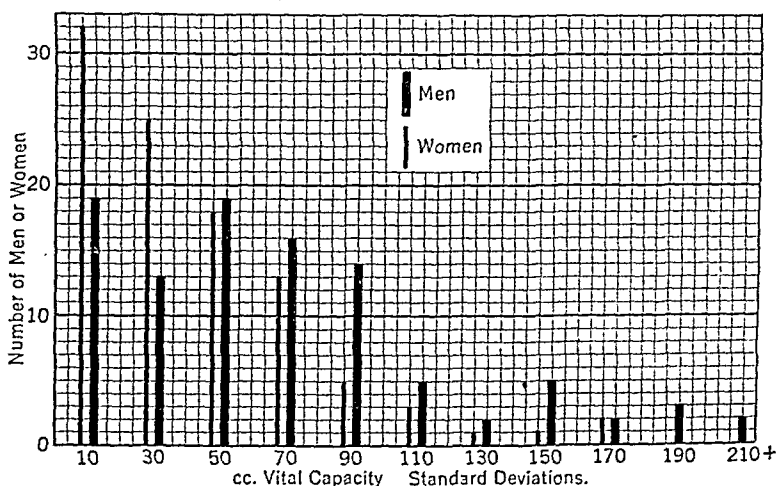
Using the regression formula $Y = a + b(x - \bar{x})$ (3) the best straight line was calculated for all of the vital capacity determinations of each student during his or her 3 or 4 years in college, and the standard deviation of the observed readings from this line was calculated in each case. The results are graphically shown (Chart 1).

Results. It will be seen that 19 of the men and 32 of the women exhibited standard deviations of less than 20 cc. from the best straight line. This group of 19 men and 32 women could be further subdivided into 10 men and 14 women who exhibited no vital capacity change whatever, 4 men and 4 women who exhibited a uniform gain, and 5 men and 14 women with small irregular variations.

Apparently the cases tend to follow a normal distribution, there being no definite tendency toward the separation of a group of

extremely variable individuals from the main group. It would, moreover, be impossible to draw an arbitrary line and say "beyond this line the variability is so great that the test is of no diagnostic value for any disease." On the other hand, it would be possible, if we knew the variations to be expected in any particular disease to say "for this disease the test might be helpful in students whose variations did not exceed such and such a figure." By way of illustration, in pneumonia the fall in vital capacity usually amounts to from 1000 cc. to 3000 cc.² The greatest standard deviation exhibited by any student in the present study was 235 cc. The vital capacity might therefore be used with propriety in any of these 200 students as an aid in the diagnosis of pneumonia.* On

CHART 1.—VITAL CAPACITY DEVIATIONS FROM YEAR TO YEAR.



Deviations are expressed in terms of the standard deviation from the "best straight line" which could be drawn through the points representing all of the vital capacity determinations of 100 male and 100 female students during their 3 or 4 years in college.

the other hand, in the early stages of pulmonary tuberculosis, where physical signs may still be indefinite and the vital capacity loss as low as 250 cc.,⁵ the test would be helpful only in those students whose vital capacities were known to vary but little; here it would be proper to exclude from consideration any whose standard deviation from the best straight line exceeded 83 cc.: this would mean the exclusion of 32 of the men and 12 of the women of the present study.

For a number of years we have used the vital capacity as an aid in the diagnosis of diseases of the thoracic organs, particularly where

* Unless the vital capacity loss exceeds 3 times the standard deviation, it is not regarded in this study as significant.

pulmonary disease was suspected. With a better understanding of what may be expected from the test there has come an increased reliance upon its dependability. While, for practical purposes, we have not found it necessary to make the actual calculations required to determine in each case whether an observed deviation exceeds 3 times the standard deviation from an individual's best straight line, yet we have learned that the principle involved is essential. When, for example, disease is suspected, and the vital capacity is found to be lower than on previous occasions, we have learned to scan the previous vital-capacity determinations in the patient's record to see whether variations comparable in magnitude have occurred in the past. If so, little or no weight is attached to the finding, even though the figure may be well below the individual's average. If, on the other hand, a similar vital capacity fall is observed in an individual whose determinations have remained comparatively constant, it is taken seriously. Used in this way, it is believed that in university health services and in offices of physicians who have an opportunity to examine their patients at intervals, particularly if their patients come to them for an annual health examination, the test will be found of value. It requires only a minute or two to carry out, is practically free from discomfort and danger, and, depending as it does upon the patient's own effort, coöperation and coördination, often throws a new and revealing light upon his psychological makeup.

Conclusions. 1. In the case of 100 male and 100 female college students, the best straight line was calculated for all of the vital capacity determinations of each student during his or her 3 or 4 years in college, and the standard deviation of the observed readings from this line was determined in each case.

2. The diagnostic value of any given vital capacity will depend chiefly upon: (a) Whether the vital capacity loss is great in comparison with previously observed variations; and (b) whether the magnitude of the vital capacity loss is commensurate with what is expected in the particular disease under consideration.

3. The vital capacity may be a valuable diagnostic procedure in university health services and in the hands of practitioners who have the opportunity of examining patients at intervals, especially where annual health examinations are made.

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THE CLINICAL USE OF DESOXYCHOLATE AND DESOXYCHOLATE-CITRATE AGARS—NEW CULTURE MEDIA—FOR THE ISOLATION OF INTESTINAL PATHOGENS.

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DIFFICULTIES in the isolation of pathogenic intestinal bacteria appear to be due in part to the shortcomings of widely used culture methods such as those of Endo, of MacConkey, and the eosin-methylene-blue medium. Other difficulties have been discussed elsewhere.²

Recently, Leifson¹ suggested the use of new culture media, based on the selective action of sodium desoxycholate, designated as desoxycholate agar and desoxycholate-citrate agar* which appear to offer greater selectivity, thus promising greater possibilities and facility in the isolation of pathogenic bacilli living in the intestine. Through association with Dr. Leifson, these media have been available to me for more than 2 years during which time I have used them both in research and in the routine clinical study of bowel disturbances. In the beginning eosin-methylene-blue and Endo's media were employed simultaneously with desoxycholate and desoxycholate-citrate agars. Later, because of the superiority of the new media, the others were not used.

Method. I have used plates of desoxycholate agar and desoxycholate-citrate agar concomitantly as follows: Material is secured directly from the bowel by means of a rectosigmoidoscope. When this is not possible, only fresh dejecta is employed. Both plates of desoxycholate and desoxycholate-citrate agars are streaked immediately after instrumentation or defecation. One-half of the desoxycholate agar plate is streaked with undiluted material. The other half is streaked with a loopful of material diluted in bouillon, since not infrequently the undiluted inoculum results in overgrowth. The desoxycholate-citrate agar plate is streaked with undiluted material usually without resulting overgrowth because, as will be noted further, the colon bacilli are considerably inhibited. The plates immediately thereafter are incubated aerobically at 37° C. for 20 to 24 hours, when they are studied.

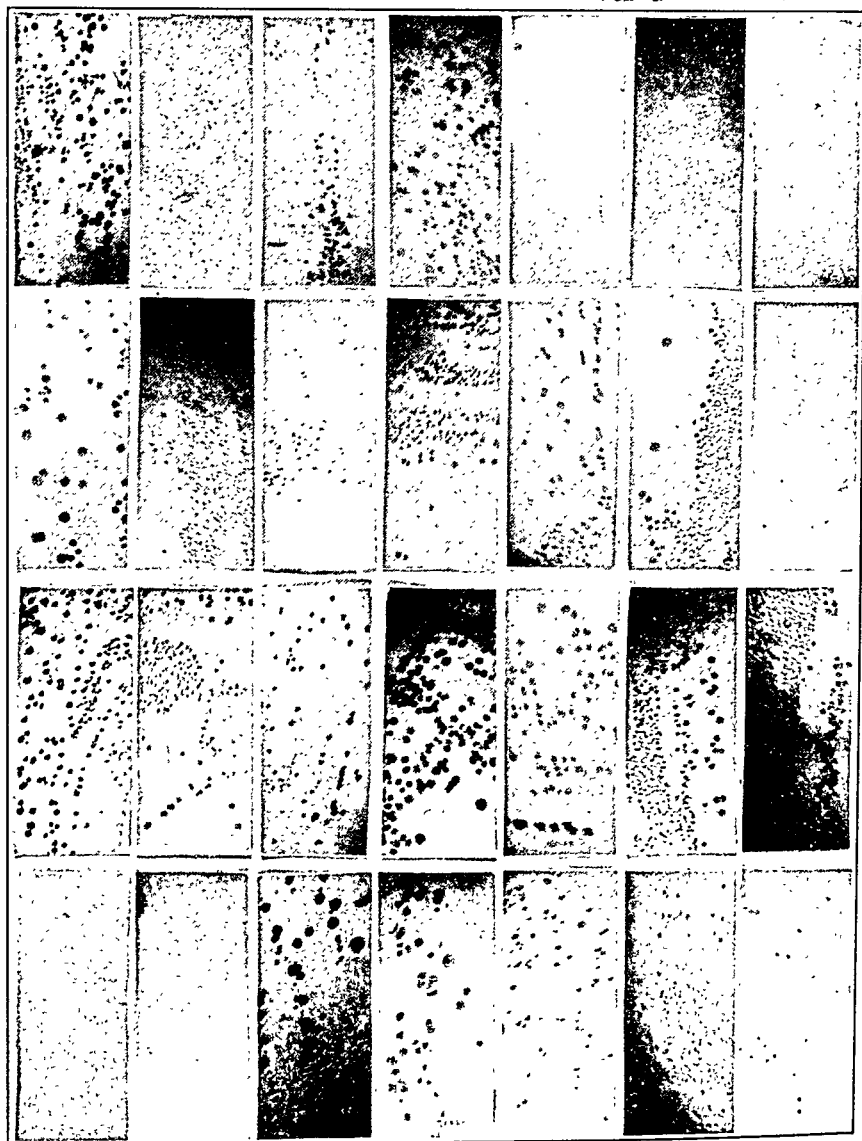
Both desoxycholate and desoxycholate-citrate agars at a pH of 7.4 inhibit all Gram-positive bacteria. This is important for two

* The composition of the media is as follows: Desoxycholate agar: water, 1000 cc.; peptone, 10 gm.; agar, 12 to 17 gm.; sodium chloride, 5 gm.; lactose, 10 gm.; ferric ammonium citrate, 2 gm.; dipotassium phosphate, 2 gm.; sodium desoxycholate, 1 gm.; neutral red, 0.033 gm.; pH 7.3 or 7.5. Desoxycholate-citrate agar: pork infusion, 1000 cc.; peptone, 10 gm.; agar, 20 gm.; lactose, 10 gm.; sodium citrate ($2\text{Na}_2\text{C}_6\text{H}_5\text{O}_7 \cdot 11\text{H}_2\text{O}$), 25 gm.; sodium desoxycholate, 5 gm.; lead chloride (optional), 3.5 gm. (1 to 300,000); ferric ammonium citrate (green scales), 2 gm.; neutral red, 20 mg. (1 to 50,000); pH 7.4. For further essential details the original paper must be consulted. Dried preparations of the media are available at the Baltimore Biological Laboratory, Baltimore, Md.

Growth of Various Types of Intestinal Bacteria on the New Desoxycholate Media and on two of the most Common Old Media.*

Organism	Des-oxycholate-Citrate Agar	Des-oxycholate Agar	Endo Agar	E. M. B. Agar
Enterococcus				
Escherichia				
Acetobacter				
Alk. thigenes				
Proteus				
Pseudomonas				
Descentory alk. thigenes				

* The author is indebted to Dr. Einar Lofson for the preparation of this plate.



Dysentery
Sonne

Dysentery
Shiga

Dysentery
Flexner

Paratyphoid B

Paratyphoid A

Typhoid

Cholera

reasons: first, it enables the use of a larger inoculum which is desirable because intestinal pathogens are rarely present in abundance; second, it eliminates streptococci and enterococci, the colonies of which often resemble those of the pathogenic bacteria on other types of media. Desoxycholate and desoxycholate-citrate agars offer striking contrasts in the appearance of the colonies of the various types of bacteria. The deep red color of the colonies of colon bacilli does not diffuse into the medium or fade out upon incubation for 24 hours. *Proteus*, the presence of which frequently makes difficult the isolation of other bacteria because of its spreading characteristics, appears as a discrete, non-spreading colony when the surface of the medium is dry.

Desoxycholate-citrate agar is striking in that it possesses some advantages not offered by any other medium in the isolation of certain intestinal pathogens. Not only does it eliminate all Gram-positive intestinal bacteria, but it inhibits markedly the common colon bacilli, alkaligenes, Duval-Sonne, and the Shiga types of dysentery bacilli. In consequence, the problem of losing those capable of growing on this medium (dysentery Flexner, typhoid, paratyphoid A and B, many other paratyphoid, suipestifer, and pyocyaneus) through dilution is obviated, since the undiluted material generally can be streaked without encountering overgrowth from non-pathogens. *Vibrio cholerae* and *Proteus* grow poorly (Fig. 1). Typhoid and Paratyphoid A bacilli present discrete, colorless, translucent colonies, while the colonies of other intestinal pathogens are colorless and opaque. *Pyocyaneus* colonies are identified by their grayish-green appearance. *Proteus* colonies are either colorless or have a brownish center.

On desoxycholate agar, practically all types of pathogenic and non-pathogenic Gram-negative bacilli capable of living in the intestine of man grow well with little or no inhibition, as compared with other types of media. As noted, Gram-positive organisms are completely inhibited (Fig. 1). *Escherichia* (*B. coli* group) appear as red colonies. *Aërobacter* colonies (*B. lactis aërogenes* group) are pink, or present red centers with a colorless periphery and are mucoid. The colonies of the non-lactose-fermenters are colorless. It is to be emphasized that these distinctions are indicative but not pathognomonic. The few available stock strains of *B. shiga* dysentery seemed to grow better on this medium than on Endo's and eosin-methylene-blue media. The limitations of desoxycholate agar are as follows: Here, like most other types of media, dilution of material is usually essential. This may result in the loss of pathogenic organisms which are rarely present in large numbers. However, this difficulty is modified by the ability to use a larger inoculum because of the inhibition of Gram-positive bacteria and by the concurrent use of desoxycholate-citrate agar, on which pathogens

referred to grow readily, Gram-positive organisms not at all, and other Gram-negative bacilli to a markedly limited degree.

The above findings are based, first, on the observation of growth on these two media, particularly of intestinal pathogens secured from stock cultures, from strains isolated from active cases, and from some of the subcultures kindly forwarded by both Drs. T. T. Mackie and Joseph Felsen of New York City. These media have been used for more than 2 years in 130 consecutive cases of bowel problems, mainly subacute and chronic, the etiology of which had been undetermined at the time of this examination.

Summary and Conclusions. New culture media designated as desoxycholate and desoxycholate-citrate agars have been applied in clinical research and in the routine clinical investigation of bowel disturbances. Both media used simultaneously inhibit to a degree not encountered in other culture methods all Gram-positive intestinal bacteria. Desoxycholate-citrate agar inhibits practically all of the common intestinal non-pathogens, growing only dysentery Flexner, typhoid, paratyphoid A and B, as well as other paratyphoid, *Pyocyaneus* and *Proteus* bacilli. *Proteus* grows as a non-spreading colony. Desoxycholate agar offsets, in a measure, the limitations of the above by growing all Gram-negative but no Gram-positive organisms. Thus, the concomitant use of both media, one complementing the other, each in part overcoming the limitations of the other, is regarded as a distinct advance in the routine clinical study of bowel disturbances from a bacteriologic standpoint.

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PLYLEPHLEBITIS OF EXTRAPORTAL ORIGIN.

REPORT OF A CASE WITH REVIEW OF THE LITERATURE.

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THE medical literature of the past 75 years is replete with reports of portal pyemia. Many large clinics have studied this condition particularly from the point of view of its relation to appendicitis,^{33,14,22,6} and it is perhaps well to be aware of this association which, although

not common, occurs frequently enough to demand clinical recognition. Despite the fact that the incidence of pylephlebitis following appendicitis is believed to be about one-half of 1%,³³ disease of the appendix is unquestionably responsible for an overwhelmingly large proportion of the number of known cases. Eliason¹⁴ reported 92.8% of a series of 14 cases, Koster and Kasman²² found 3 of 4 cases, and Brown⁶ originally reported 42% of 46 cases as related to appendicitis.

Nevertheless, one should also bear in mind that portal drainage is not limited to the appendiceal area. Instances of portal pyemia have been reported as resulting from suppuration in practically all of the organs and areas drained by the radicles of the portal vein. It has occurred with disease of the stomach,^{4,18,37,7,36} duodenum,^{7,10,31} small intestine,^{6,27} colon,^{7,23,24,26} rectum,^{6,7,16} pancreas,^{15,36} spleen,^{16,25,5,28} gall bladder,^{22,7,10,5,8,30,3,36} and mesenteric glands,^{6,16,19} Certainly the fact that pylephlebitis may result from so many sources is no more than one would expect, since the term itself is taken to imply an inflammatory or infectious lesion involving the portal vein which may arise in any organ drained by the portal system. Except for the very rare instances which we shall mention later, all of the reported cases of portal suppuration fulfill the requirements of this accepted and limiting definition.

Clinical Picture.—The diagnosis^{33,6,29} of pylephlebitis will be made with ease if one keeps in mind the fact that this condition is practically never primary or spontaneous, but always follows some infective process in an organ or area drained by the portal system, including all of its radicles and anastomoses. The signs and symptoms of pylephlebitis, therefore, must be superimposed upon, and modified in any individual case by the nature of the disease which originally resulted in portal sepsis. The triad of (1) evidence of the primary cause (2) followed by the picture of sepsis (especially chills and sweats) and (3) evidence of involvement of the liver should make one consider this diagnosis.²⁹

The onset is commonly sudden, often being ushered in by shaking chills with or without abdominal pain. Occasionally vomiting or distention may initiate the disease. The chills are more severe at the onset, followed by fever and sweats, and tend to disappear as the patient fails. Within a matter of days evidence of involvement of the liver, such as pain, jaundice, or right upper quadrant tenderness appears.

The patient presenting the picture of "abdominal facies," looks very ill and distressed. Fever is usually high with a rapid pulse and quickened respirations. In the majority of cases the liver is slightly or greatly enlarged, firm, smooth, and tender to palpation. When the liver is of normal size, there is often tenderness on deep palpation in the right upper quadrant. Occasionally, a friction rub over the liver may be heard. Half the cases show jaundice to a varying degree. Enlargement of the spleen has been noted in about 20% of

the instances. Abdominal tympanites is often present, and may interfere with proper examination of the abdomen. Ascites, hemothemsis or other evidence of portal obstruction occur when a thrombosis is superimposed upon the suppurative lesion present in the portal vein. Diarrhea or vomiting may occasionally be troublesome.

A valuable clue to involvement of the liver may at times be found in evidence of infection of the right pleura, diaphragm, or right lower lung. This infection probably results because the lymphatic drainage from the peritoneal cavity through the right diaphragm is much more abundant than that through the left diaphragm.²⁶ Infection in the right lower lung and pleura commonly follows gross sepsis of the liver or subphrenic space which had been present for a week or longer.²⁹ Hence hiccoughs, a friction rub heard over the right pleura, pain referred to the right shoulder, limitation of movement of the right diaphragm³³ on fluoroscopy, or evidence of infection in the lower lobe of the right lung can be taken as supportive evidence of the fact that the liver is involved. Rarely this evidence may be present on the left side.²⁹ The enlarging liver may also elevate the diaphragm, cause¹⁰ collapse of the lower lobe of the right lung, and produce signs of atelectasis.

The patient becomes weaker, loses weight, and often lapses into a coma before death. The disease may terminate in a few days or may rarely continue for a month or two. Leukocytosis is common. Prolonged cases show a progressive anemia. Blood cultures almost invariably remain sterile unless the hepatic veins become infected. There are no characteristic urinary changes. The prognosis is poor in most instances.

It is important that this disease be differentiated from multiple or single abscesses of the liver and subphrenic abscess, which conditions may occasionally be amenable to surgical treatment. Edema of the chest wall or over the right upper quadrant, definite fluctuation over the liver area, or palpable irregularities on the liver surface favors the diagnosis of hepatic suppuration.²⁹ Evidence of gas under the diaphragm favors the diagnosis of subphrenic abscess.

Anatomy of the Collateral Circulation.—It is of significance to recall the existence of points of communications between the portal and systemic circulations, and to realize that these anastomoses may serve as pathways from which portal sepsis may result, despite the fact that the lesion may be situated in an organ drained primarily by the systemic circulation. This concept will perhaps be more generally recognized if one considers the venous channels through which a compensatory circulation may be established in instances of portal obstruction. For the sake of clarity it may be of some value to review these anatomical relationships.

In the event of the portal obstruction (*i. e.*, portal cirrhosis of the liver) collateral circulation may be established through the fol-

lowing channels:^{6,17,34} (1) The veins of the esophagus open into the azygos vein and also communicate, at the gastric orifice, with the gastric veins and thus with the portal circulation. (2) Very rarely the ductus venosus remains patent, thus affording a direct communication between the portal vein and the inferior vena cava. (3) The veins which originate in the intestinal walls provide a subperitoneal plexus of anastomoses between the branches of the portal vein and the inferior vena cava (System of Retzius). (4) The origins of the superior hemorrhoidal vein, a branch of the inferior mesenteric, anastomose with the inferior hemorrhoidal which opens into the hypogastrics. (5) The communications between the retroperitoneal veins opening into the lumbar and azygos veins, and the veins of the peritoneum occur especially where, as in the case of the duodenum, pancreas, and colon, areas drained by the portal vein are bound to the abdominal parietes. The veins of the left kidney anastomose to some extent with the veins of the descending colon, and venous trunks may put the renal vein itself in communication with the left colic vein.³⁴ The veins of the descending colon may communicate with the spermatic plexus.² A communicating branch of the left renal vein has been seen and reported.²¹ Virchow observed a similar anastomosis between the splenic and azygos veins.³⁵ (6) The branches of the accessory system of Sappey pass in the round and falciform ligaments (particularly the latter) to unite with the epigastric and internal mammary veins, and, though the diaphragmatic, with the azygos. The paraumbilical vein may pass from the hilus of the liver by way of the round ligament to the umbilicus.

Extraportal Foci.—It would seem obvious that these anastomoses which are capable of establishing a compensatory circulation in instances of portal obstruction are also potential pathways for the development of portal pyemia from points drained by the systemic circulation.

Several instances of pylephlebitis have been reported which have been dependent upon portal-systemic anastomosis for their production. Frerichs¹⁶ and von Schuppel³² have each reported a case of portal pyemia following ligature of the umbilical vein. More recently White³⁸ recounted another instance following umbilical infection in an infant 16 days old. Cantlie⁹ mentions that this condition is common in China. Other instances are also recorded in the literature.^{5,36}

Almost without exception these reports deal with the occurrence of umbilical infection in the newborn. It seems likely that in these circumstances sepsis of the portal system occurred by way of the umbilical vein. Although lesions of this type are most uncommon in this day of aseptic care, the case reported by White indicates that it may still be seen occasionally. One would hardly expect this to occur once obliteration of the umbilical vein had taken place, but

it should be remembered that even then the paraumbilical veins still provide a connection with the portal system.

Edwards¹³ reported an unusual case of suppurative pylephlebitis associated with a carcinoma of the esophagus. Since the esophageal lesion was situated 3 inches above the cardiac orifice, it seems clear that the secondary suppuration which occurred could not have involved the portal vein directly. Infection of the portal system must have been dependent upon the anastomosis between the veins of the lower esophagus and the veins of the stomach.

At least 3 cases of portal pyemia following sepsis of the female genital tract have been recorded. DeSilva's case¹² resulted from suppuration of an ovarian cyst and pyosalpinx. Bryant⁷ reported 2 cases, 1 following a septic abortion, and another associated with a pyosalpinx. The possible connection between the spermatic plexus and the veins of the descending colon has already been noted. In the female a similar communication may exist between the uterine plexus and the veins of the descending colon. These 3 cases may be taken as examples of portal pyemia resulting from anastomoses of this type.

Of particular interest to us is the free communication between the portal and systemic circulations existing in the hemorrhoidal plexus. We have recently had the opportunity to observe a patient with pylephlebitis directly attributable to a suppurative process in the testis and scrotum. We believe this to be the first reported instance of the development of portal pyemia from this focus. The case proved to be still more unusual in that death occurred in uremia; the patient thus exhibiting a liver-kidney syndrome.

Case Report. A 43-year-old stuporous white male was admitted to the hospital on February 5, 1934. A meager history was obtained from the family. It appeared that the patient had enjoyed only fair health, and for the past year had complained of a persistent cough which was worse in the morning and productive of purulent sputum. The patient believed this to have started as a "cold." He had also lost 10 pounds in weight and had had frequent night sweats during the past year. A history of syphilis with subsequent outpatient treatment was obtained. An attack of painless jaundice of several weeks' duration followed arsphenamine therapy 9 months before his final admission to the hospital. This cleared completely and resulted in no symptoms other than jaundice. Further antiluetic treatment was discontinued. Gonorrhea was denied, as were other infections of the genitourinary tract.

From this point on the patient had continued in his usual health until 2 weeks before entry to the hospital. At this time he developed a severe, constant, non-radiating pain in his scrotum which became swollen, tender, and warm to touch. After 1 week he was admitted to a surgical service of this hospital where conservative local treatment was instituted. While on the surgical wards he developed repeated chills and fever, and after 4 days, became jaundiced and drowsy. Three days later he was transferred for medical treatment.

Physical examination revealed a jaundiced, semicomatose well developed, but poorly nourished white male hiccupping continually. The skin was smooth, warm, and moist, and the lips were cyanotic. The pupils

reacted sluggishly to light, and the eyegrounds were normal in appearance. The nose, mouth, and pharynx were not remarkable, no evidence of bleeding was noted. The right upper chest was dull to percussion, with exaggerated breath sounds, and many moist râles; both lower chests posteriorly were dull to percussion with bronchovesicular breath sounds, and fine crackling râles of patchy distribution. The temperature was 101° F., the respirations 24, and the pulse of 88 was of very poor volume. The blood pressure was 105 mm. of Hg systolic and 70 diastolic.

No evidence of cardiac lesions was noted. The heart was not enlarged, the sounds were regular and of fair quality, and the peripheral veins were not distended. Clubbing of the fingers and cyanosis were present.

The abdomen was distended and tympanitic, and a firm, tender, smooth liver edge was palpable 6 cm. below the costal margin. A firm, non-tender splenic margin was made out 12 cm. below the costal margin. No signs of fluid were elicited nor was there any evidence of portal obstruction.

The scrotal sac was swollen and fluctuant, with a large ulcerated area 2 inches in diameter on the inferior posterior surface through which the testicles could be seen, and through which pus oozed continually.

On entry to the hospital the patient showed a normal renal output. The urine had a specific gravity of 1.024, a strong trace of albumen, bile, no sugar or acetone, and a few hyaline casts in the sediment. The hemoglobin was 70%, the leukocyte count 5700 of which 89% were neutrophils. The blood non-protein nitrogen which was 120 mg.% on his admission to the medical service rose to 250 mg.% 24 hours later, and a progressive oliguria was noted. The free blood cholesterol was reported as 38 mg.% with no ester cholesterol. The icteric index was over 100, and the blood Kahn test was negative.

The patient's condition was obviously extremely poor, and despite supportive measures, he lapsed into a quiet coma, and died 24 hours after being transferred to the medical service.

Autopsy Findings. Summary of postmortem examination (17 hours after death, Dr. J. P. Sheehan).

Generalized jaundice. No edema. A large ulceration 5 cm. by 3.5 cm. in diameter was seen through the wall of the scrotum, exposing the testes. The edges of the ulcerated area were blackish in appearance with a thick yellow-green exudate on the exposed surfaces. Moderate clubbing of the fingers was noted.

Peritoneal Cavity: Appendix was negative. About 100 cc. of clear orange-yellow fluid was present in the pelvis. No free pus or adhesions were noted. The mesenteric nodes were not palpable.

Pleural Cavity: Adhesions at both apices. No free fluid or pus.

Pericardial Cavity: Normal.

Heart: Weight 380 gm. Muscle, coronary arteries, and valves were within normal limits.

Lungs: Left, 820 gm.; right, 1200 gm. A firm mass was palpable in the lower portion of the right upper lobe. Section through this mass revealed an area irregularly traversed by dense bands of white connective tissue with widely dilated bronchi and bronchioles. The terminal portions of these structures ended in cavity-like areas with thick dark green and dark red walls containing yellowish curdy material. No nodules were noted in the walls of the cavities or in the surrounding tissue. Some of the cavities were situated close to the pleura. The apical portion was free. Blood was expressed from the upper lobes, and bloody frothy fluid from the lower lobes. The bronchial mucosa was intensely dark red, and a purulent-appearing exudate was noted in the bronchi.

Spleen: Weight 1520 gm. Almost 5 times normal size. Moderately soft, with pinkish-gray and purplish-gray smooth surface. The cut surface

was dark red and reddish-purple. Much of the spleen was soft with an abundance of pasty dark red scrapings. The trabeculae were obscured. The splenic vein was not thrombosed.

Gastro-intestinal Tract: Normal in its entire length from esophagus to rectum.

Liver: Weight 3180 gm. Surface irregular with shallow depressions. The color was dark reddish-gray with numerous green areas embracing smaller yellowish ones. Some small (2 mm.) yellowish areas were noted in the reddish-gray portions. The cut surface revealed that all the branches of the portal vein in the liver were outlined by a strip of dark green tissue 5 to 11 mm. deep around the veins. Yellow areas (2 to 3 mm.), some soft were noted in the dark green areas, from which thick green fluid escaped. The rest of the liver tissue was light greenish-brown in appearance with darker brown central areas. Much purulent-appearing material was noted in the larger branches of the portal radicles.

Gall Bladder and Bile Ducts: Normal.

Pancreas: Normal.

Kidneys: Combined weight 500 gm. Definitely enlarged and swollen. Capsule stripped with ease. Cortex was increased to 11 mm. in thickness. Kidneys were a pale gray-greenish color. No petechial hemorrhage. Pelvises and ureters were normal.

Adrenals: Negative.

Bladder and Prostate: Negative.

Genital Organs: The left testicle and epididymus formed a large, very firm mass 8 by 6 by 6 cm., in which the testicle and epididymus could not be identified. On section, this mass was seen to be irregularly traversed by bands of dense white connective tissue, in which 3 or 4 dark green and yellow-gray lined cavities (about 1.5 cm.) were noted, especially at the lower portion. Yellow and white firm circular areas (1.0 by 1.5 by 1.0 cm.) were noted in the region once occupied by the epididymus. The tunica vaginalis was thickened. No nodules were made out throughout the mass. The cavities noted above were seen to communicate in part with the tunica vaginalis and the exterior through the scrotal wall. The right testicle was negative.

Aorta: Yellow deposits of atheroma throughout aorta. No calcification or scarring.

Cultures: Because of the delay in performing the autopsy, cultures of the liver and scrotum were unsatisfactory.

Microscopic Examination. Microscopic examination of the tissues was essentially negative with the following exceptions:

Lungs: These showed a picture consistent with bronchiectasis, bronchitis, bronchopneumonia and edema.

Spleen: Evidenced marked congestion. Clumps of lymphocytes and large mononuclears were noted between the Malpighian corpuscles. Fibrosis was seen in one corpuscle, and hyaline pigment in others. Numerous neutrophils, plasma cells, and large mononuclears were seen in the pulp.

Liver: Showed large and small areas of necrosis with massive infiltration by neutrophils and a few large mononuclears. At the periphery of these masses of cellular infiltration, bile ducts and blood-vessels above remained. The intervening lobules were compressed with the cell cords running parallel rather radially. Marked engorgement of the central veins and sinusoids was present. In some areas the central veins stained eosinophilic with nuclei absent. In one area only the outline of the liver cells persisted with massive infiltration by neutrophils at their periphery. In some portal areas infiltration by lymphocytes and a few neutrophils was noted.

Pancreas: Slight increase in connective tissue about the ducts and islets.

Kidneys: Minor degrees of tubular swelling and degeneration were noted.

The glomeruli were normal throughout. Severe necrosis was absent. No hemorrhagic areas were seen.

Testicle and Epididymus: They constituted a mass of fat and fibrous tissue with numerous blood-vessels and one nodule of gland tissue diffusely infiltrated with lymphocytes, neutrophils and large mononuclears. A mat of fibrin with numerous neutrophils was seen at the edge of the section. Fibrin masses were present in the tissue.

Anatomical Diagnosis. Pylephlebitis with miliary liver abscesses.

Bronchopneumonia (lower lobes, both sides); bronchiectasis (right upper lobe); acute bronchitis; healed pleuritis; acute and chronic inflammation of left testicle and epididymus; bile nephrosis.

Discussion.—One of the prominent features of this case is the presence of a suppurative lesion involving the epididymus, testis, and scrotum. The occurrence of a genital lesion of this type presents etiologic problems which remain more or less difficult to explain. Caulk,¹¹ in 1927, reported 15 cases of abscess of the testicle which he had personally observed. He pointed out that lesions of this type may occur in about 5% of the cases of epididymitis, and he also mentioned pyelonephritis, prostatic obstruction, cystitis, prostatitis, and seminal vesiculitis as additional causes. Barney¹ previously reported 3 cases of abscess of the testicle in none of which was there a demonstrable etiologic factor. It is his belief that it is very rare to have a suppurative testicular lesion without epididymal involvement. Although both of these authors recognize that an infection may be transmitted to the testicle by way of the blood stream or the lymphatics, a septic lesion of the genitourinary tract itself is looked upon as being the most likely source. Caulk,¹¹ in fact, regards the spread of infection along natural channels (that is, vas and epididymus) as the most frequent cause of testicular suppuration. It becomes necessary then for us to assume that the genital lesion in our case in all probability started in the epididymus. Although it is barely possible that this lesion may have been blood borne from the bronchiectatic process in the upper lobe of the right lung, it seems more plausible to assume that the original epididymal involvement was due to a pre-existing genitourinary lesion which we were unable to demonstrate.

From this point on there follows a close relationship between the sequence of events clinically and the pathologic findings.

It is our belief that the presence of pylephlebitis can be best explained on the basis of direct extension from the suppurative genital focus. Although it is conceivable that a septic lesion in an area drained primarily by the systemic circulation may produce sepsis elsewhere, it seems clear that when this does occur it would produce a bacteremia or generalized septicemia rather than a suppurative lesion of the portal system. It also follows that pylephlebitis itself cannot produce septicemia unless the lesion extends beyond the hepatic veins. Our conclusion then that portal pyemia in

this instance was due to direct extension from the septic genital focus seems to be reasonably justifiable.

We are finally confronted by the problem of explaining the mechanism of production of pylephlebitis on this basis. Careful attention to certain otherwise essentially unimportant anatomic features reveals that this may occur by one of two routes. We have mentioned the presence of a free communication between the portal and systemic circulation which exists at the hemorrhoidal plexus. It will also be recalled that the coverings of the testis and scrotum are drained in part by the internal pudendal vein which communicates with the hemorrhoidal plexus by way of the inferior hemorrhoidal vein (see diagram). This communication seems to be a more likely route than the occasional connection which may exist between the veins of the descending colon and the spermatic plexus.

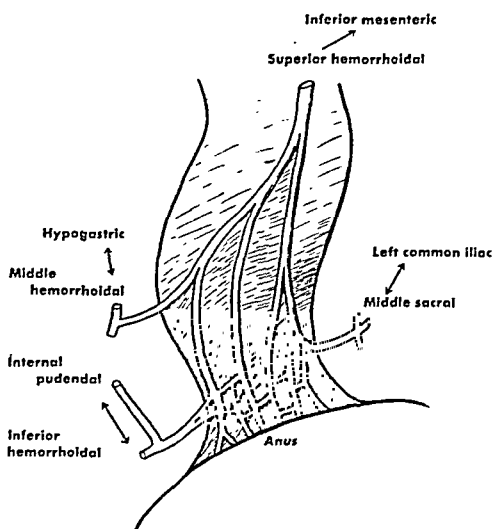


FIG. 1.—Anastomosis between the portal and systemic circulation at the hemorrhoidal plexus. Modified from Poirier, P., and Charpy, A.: *Traite d'Anatomie Humaine*, vol. 2, Masson et Cie, Paris, 1901, p. 4006.

Thus we may view this case as probably the first reported instance of the occurrence of pylephlebitis due to an extraportal focus in the testis and epididymus.

An additional point of interest is the resemblance of the terminal symptoms of this case to those of the liver-kidney syndrome as described by Helwig and Schutz.²⁰³ These authors pointed out that several days following either trauma or infection of the liver there may develop a syndrome characterized by jaundice, mucous membrane bleeding, prostration, oliguria with urinary albumen and casts, nitrogen retention in the blood, terminal anuria, coma, and death in uremia. At autopsy the kidneys, grossly and microscopically,

may show varying degrees of nephrosis. The kidneys in our patient showed evidence of nephrosis, while the laboratory findings and the clinical picture were quite typical. Helwig and Schutz^{20b} recently reported an instance of pylephlebitis secondary to a ruptured appendix which terminated in death by this syndrome. Except for the primary focus this case resembles very closely the one herein reported. We have found no other case of pylephlebitis in the literature in which a similar termination was mentioned, nor have any of the reported cases shown the presence of azotemia.

It will be recalled that our patient had had a previous illness which unquestionably resulted in liver drainage. Although the extent of this injury due to arsphenamine cannot be estimated, it is entirely within the realms of probability that the subsequent occurrence of additional liver damage was sufficient to produce a typical liver-kidney syndrome.

Summary.—A case of pylephlebitis is reported in which the infection originated in a focus in the systemic circulation. The anatomy of the portal-systemic anastomoses is reviewed and its clinical significance discussed. The reported cases of pylephlebitis of extraportal origin are reviewed.

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PRIMARY TUBERCULOUS APPENDICITIS AND APPENDICITIS COMPLICATING PULMONARY TUBERCULOSIS.

By E. T. THIEME, M.D.

(From the Department of Surgery, University of Michigan.)

TUBERCULOUS appendicitis is a relatively rare condition either in healthy people or in those with known pulmonary tuberculosis, while pyogenic appendicitis as a complication of pulmonary tuberculosis is not uncommon. It is the purpose of this paper to present a study of: 1, so-called "primary" tuberculous appendicitis and 2, appendicitis complicating pulmonary tuberculosis. To this end the cases of tuberculous appendicitis in patients without known pulmonary disease at the time of their operation and the cases of pulmonary tuberculosis complicated by appendicitis seen in the University Hospital during the past decade have been followed.

So-called "Primary" Tuberculous Appendicitis. During this period there were 7 cases of tuberculous appendicitis occurring in patients without the recognition of tuberculosis elsewhere at the time of the operation.

This condition, although rare, has been well described in the literature. Its incidence has been given variously from 0.3 to 3% of all appendicitis, depending upon the thoroughness with which the routine pathologic examination has been done. The pathologic picture is divided into 3 generally accepted types: 1, tuberculous peritonitis, 2, the more common ulcerative appendicitis, in which the mucosa and submucosa show a varying number of tubercles with ulcerations of varying depth and size, and 3, the hyperplastic type with diffuse thickening and marked connective tissue proliferation without caseation. The route of infection has been considered as hematogenous, lymphatic, or by direct infection from contaminated feces.

Following the pathologic report of tuberculous appendicitis a further study revealed pulmonary tuberculosis in 2 of our 7 cases. These 2 cases are not, therefore, examples of primary tuberculous appendicitis. This low incidence of pulmonary tuberculosis has not been the general experience and may account for our more encouraging results in this group.

That the clinical course of acute tuberculous appendicitis is not to be differentiated from pyogenic appendicitis is generally agreed; on the other hand chronic tuberculous appendicitis has been characterized by Drissen and Zollinger² as having a longer than average duration without perforation or peritonitis, and often accompanied by diarrhea. In 5 of the 7 cases the symptoms were of recurrent appendicitis, not to be distinguished in course or physical findings from the ordinary pyogenic infection. Of the remaining 2 cases, 1 was acute and had nothing in the history or clinical findings to distinguish it from a pure pyogenic infection, except perhaps a

leukocytosis of 21,000 and a temperature of 101° F. with minimal physical signs; the other was a ruptured appendix with abscess formation. From our experience there was no criterion from which a pre-operative diagnosis of tuberculous appendicitis could be made. No evidence of local tuberculosis was recognized at the time of the operation and the pathologic report came as a distinct surprise.

Postoperative, 5 of the 7 had entirely uneventful courses, 1 had a severe wound infection, and the patient with the ruptured appendix with abscess developed a fecal fistula which drained for 5 months. Inasmuch as no pulmonary disease was suspected in these 7 cases, nitrous oxide and oxygen anesthesia was used, alone in 2, and supplemented by ether in 5.

Of the 7 patients 6 have been followed; of the 2 with pulmonary tuberculosis one is still under sanatorium care 5 years later, but making satisfactory progress. The other, almost 4 years later, is married, has had a healthy child and reports herself in good condition. Neither have had abdominal symptoms such as are associated with intestinal tuberculosis. The other 4 are alive and well, 7, 3, 1½, and 1 year respectively after operation.

Since the original survey of the literature in 1910 by Muller,⁵ the prognosis of so-called primary tuberculous appendicitis has been regarded as bad, and the more recent surveys of Koster and Kasman⁴ have done little to improve this impression. However, judging from this small series of 7 patients, we cannot help but feel that the outlook must be considered as not entirely unfavorable.

Appendicitis Complicating Pulmonary Tuberculosis. This study includes 20 cases of pulmonary tuberculosis under treatment, upon whom an appendectomy was performed for appendicitis, acute or recurrent.

Many autopsy statistics* have proved that from 60 to 90% of the patients dying from advanced pulmonary tuberculosis have intestinal tuberculosis. Most authors writing on clinical appendicitis complicating pulmonary tuberculosis regard the process as pyogenic and not to be differentiated from appendicitis in non-tuberculous patients. That a distinction should be made is shown by the fact that our poor results were in those cases of pulmonary disease, poorly controlled, and who had, as was to be expected, tuberculous appendicitis.

Of the 20 cases studied, 13 were operated on for acute and 7 for recurrent appendicitis. Sleffens states that the symptoms of appendicitis in tuberculous patients are clear cut and that the indications for operation are the same as in non-tuberculous patients. From our experience, we are quite in accord with this view, as the clinical course and physical findings were those usually found in acute or recurrent appendicitis, the only exception to this being a uniformly elevated leukocyte count of 16,000 or more, regardless of the duration of symptoms.

* Pathological Report, Henry Phipps Institute Report, 1907-1908.

The postoperative course was uneventful in 12 of the 20 cases, 6 had wound infections, 1 developed pneumonia and thrombophlebitis, and there was 1 operative death. There were no fecal fistulæ in our series, which is unusual, since this complication was of frequent occurrence in other reported cases.^{2,5} The immediate postoperative pulmonary condition of all remained satisfactory despite the large variety of anesthetics used. Local or spinal is uniformly advocated and ether condemned, but the following anesthetics were employed.

Nitrous oxide and oxygen and ether	7
Nitrous oxide and oxygen	4
Nitrous oxide and oxygen and local	3
Spinal	2
Local	1
Spinal and nitrous oxide	1
Avertin and nitrous oxide	1
Avertin and nitrous oxide and ether	1
	<hr/>
	20

Kinghorn,³ reporting his experience in sanatorium patients, found only 25% of appendicitis on a tuberculous basis. Our figures are much the same, 6 of the 20 or 30% having tuberculous appendicitis, 4 acute and 2 recurrent. As stated in the pathologic concept given, intestinal tuberculosis and appendicitis may be expected in advanced poorly controlled pulmonary disease. This is emphasized when we find that 4 of the 6 cases of tuberculous appendicitis were doing poorly, having positive sputum; and 5 of the 6 had histories of continual abdominal discomfort, poor appetite and bouts of nausea. On the other hand, of the 14 with simple pyogenic appendicitis, all were doing well as far as their pulmonary condition was concerned only 3 having positive sputum. Therefore, if the pulmonary condition is controlled the appendicitis is probably pyogenic and is not associated with intestinal tuberculosis; conversely, if the pulmonary condition is uncontrolled and there is positive sputum, the appendicitis is probably tuberculous.

The follow-up studies bear out the seriousness of tuberculous appendicitis with uncontrolled pulmonary disease, since 6 of the cases so complicated, 5 are dead and the sixth is still under sanatorium care 3½ years later. Of the 5 dead there was 1 operative death, and 1 patient killed himself in despondency over his ill health. Two died 2 months after, and 1 a year and a half after the appendectomy from widespread tuberculosis. Therefore, in advanced pulmonary tuberculosis, appendicitis may be expected to be on a tuberculous basis, and if so, the prognosis is very bad.

In contrast, of the 12 cases of pyogenic appendicitis followed, 10 are alive. One died of his pulmonary disease, the other during a third stage thoracoplasty 1 year after the appendectomy. Of the 10 living, 5 are still under sanatorium care and progressing satis-

factorily and 5 have been discharged as arrested cases. Subdividing the cases of acute pyogenic appendicitis, 4 have been discharged as arrested; of the 4 operated for recurrent appendicitis, only one has been arrested.

Muller,⁵ Kinghorn,³ Armstrong,¹ and others in dealing with pulmonary tuberculosis have advocated appendectomy in cases with chronic intestinal disturbances to remove a source of irritation and often a tuberculous focus. Some have reported great improvement. As far as removing a tuberculous focus was concerned our results certainly do not warrant the procedure, since 5 of the 6 with tuberculous appendicitis in this group are dead.

Kinghorn,³ Sleffens⁷ and others have found no increase in the operative mortality in appendicitis with pulmonary tuberculosis and advocate immediate operation in acute appendicitis, selective operation in recurrent appendicitis. Our experience in general is in accord with this opinion.

Summary. Seven cases of so-called primary tuberculous appendicitis are reported, of which 2 were later found to have tuberculosis elsewhere. The history and physical findings in these 7 cases were essentially the same as in pyogenic appendicitis and the diagnosis was not made pre-operatively. The prognosis was uniformly good.

Twenty cases of pulmonary tuberculosis operated upon for appendicitis were reviewed; the lesion was acute in 13 and recurrent in 7. Of the 20, 6 had tuberculous appendicitis; 5 of them were doing poorly pre-operatively from their pulmonary standpoint. Of the 6, 5 are dead and the sixth is critically ill. The extremely poor prognosis of tuberculous appendicitis in advanced, uncontrolled pulmonary disease is evident. The 14 cases of pyogenic appendicitis occurred in patients who were doing well from the standpoint of their pulmonary tuberculosis. Their subsequent course has been such as to lead us to believe that their appendicitis was unrelated to their tuberculosis, and did not affect the course of that disease.

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BOOK REVIEWS AND NOTICES.

THE LIFE AND CONVICTIONS OF WILLIAM SYDNEY THAYER, PHYSICIAN. By EDITH GITTINGS REID. Pp. 243; illustrated. New York: Oxford University Press, 1936. Price, \$2.50.

ENTHUSIAST, perfectionist, loyalist, partisan, the essence of a gentleman in the highest sense, combined with a highly developed New England conscience, Dr. Thayer's vivid personality stands out in bold relief in these all-too-few pages. Quotations from his copious diary are numerous and well chosen; they are so revealing that the reader craves for more. But, granted that the 17 months of the Russian Red Cross mission and the war work in France "make an exciting section of the book," some will regret that they forced the rest of the Life into little more than half the total space. For instance, if "the life of Dr. Thayer reflected more clearly than that of any of his colleagues the story of the first years of the Johns Hopkins Hospital and Medical School" (Welch's opinion), 26 pages can hardly do justice to such an interesting and important period. However, the virtues of the presentation and Mrs. Reid's well known skill in biographical composition far outweigh such criticism. For those who knew Dr. Thayer well these sympathetic pages constitute a satisfying record, while adding occasional hitherto unknown details; for those about to make his acquaintance through these pages a figure of unusual strength of character, charm of personality and professional attainment will be disclosed. E. K.

DIETETICS FOR THE CLINICIAN. By MILTON ARLANDEN BRIDGES, B.S., M.D., F.A.C.P., Director of Medical Detention, Rikers Island and West Side Hospitals, New York; Consulting Physician, Seaview Hospital, Staten Island, N. Y., etc. Pp. 1055. Philadelphia: Lea & Febiger, 1937. Price, \$10.00.

THE first edition of this work was described by the Reviewer as deserving emphatic recommendation. His judgment continues to be confirmed by the popularity of the work which has led to a third edition within less than 4 years. The new volume, greatly amplified and in part rewritten, is an improvement on its predecessors. R. K.

LA PONCTION DE LA RATE. By P. ÉMILE-WEIL, Médecin des Hôpitaux, P. ISCH-WALL, Assistant à l'Hôpital Tenon, SUZANNE PÈRLES, Chef de Laboratoire à l'Hôpital Tenon. Pp. 148; 23 illustrations, some in colors. Paris: Masson et Cie, 1936. Price, 35 fr.

WITH few exceptions (Achard, Widal, Nicolle) diagnostic puncture of the spleen (splenic biopsy) has not been practised routinely outside of Spain and Italy. The authors have sought to remedy this situation, and have come to the conclusion that with proper precautions and avoiding a few contraindications, the complications of hemorrhage and spread of infection are quite negligible. They have found the method very useful in diagnosing obscure splenomegalies and believe that even in primary blood diseases it may afford evidence that bone-marrow biopsy does not produce. A number of cases with colored illustrations are presented in support of their views. E. K.

ELEMENTARY PATHOLOGY. An Introduction to the Process of Disease. By KEITH S. THOMPSON, Pathologist, Selly Oak Hospital, Birmingham; Formerly Lecturer in the Department of Pathology, University of Birmingham and Pathologist, Queen's Hospital, Birmingham. Pp. 74; 29 illustrations and 3 colored plates. London: H. K. Lewis & Co., Ltd., 1936. Price, 10/6.

THIS is an interesting attempt—the first of its kind that we have seen—to bridge over the gap between a student's notebook and the modern imposing textbook of pathology. The author starts from the sound premise that the majority of students are so much occupied in writing notes that they are less able to comprehend and absorb what the lecturer is saying and that often their notes miss important parts of the lecture. He has therefore prepared a richly illustrated, concise outline of general pathology with, for each page of text, at least one blank page on which the student can make his notes. The brevity of the work makes it easier to read the subject of the day in advance. In England, where students begin work in the wards coincident with the study of pathology, the book should be more useful than in this country where the course is differently arranged. Though we doubt its practicability in our own course, we would like to see it tried out by an intelligent student who did not neglect the study of his textbook as well.

E. K.

GREEK MEDICINE. Volume XVIII of *Clio Medica*. By FRED B. LUND, M.D., Boston, Mass. Pp. 161; 7 illustrations. New York: Paul B. Hoeber, Inc., 1936. Price, \$2.00.

THIS excellent monograph is the eighteenth of the historical series "*Clio Medica*," which Hoeber is bringing out in handy pocket form under the editorship of Dr. Krumbhaar. Though the study of medicine and surgery long antedated the Greeks, they were the ones who established it on the footing to which our practices may be traced. In fact, as Lund states, to Hippocrates may be given the credit for freeing the art from the trammels of superstition and magic and putting it on a common-sense and even a scientific basis. What went before belongs more to the student of archæology than of medicine.

With our present-day knowledge of biology and chemistry we have a medical foundation which can no more be contradicted than the sphericity of the earth and its revolution around the sun. Greek medicine, on the other hand, came into existence when practically nothing was certain except the problems of mathematics. In fact another 150 years had to elapse after Hippocrates before even the principle of the lever was demonstrated by Archimedes, thus dispelling the not uncommon idea that it worked magically. Under the circumstances it is remarkable how successful these progenitors were in developing lines of thought, establishing a terminology and even setting the stage for what has come about in the way of saving of life, easing pain and making living a pleasure.

This little volume has surely accomplished the purpose of the Editor, namely, to present this notable era from Hippocrates to Galen in concise, yet interesting and well-rounded form.

J. W.

DIE VERERBUNG INNERER KRANKHEITEN. By PROFESSOR DR. WILHELM WEITZ, Direktor der II. Medizinischen Klinik und Poliklinik an der Universität Hamburg. Pp. 197; 67 illustrations and 12 tables. Stuttgart: Ferdinand Enke, 1936. Price, Paper, Rm. 13; Bound, Rm. 14.60.

AN interesting and valuable collection from the world's medical literature of the available data on the heredity of internal diseases, together with numerous observations made by the author in this field during the past 15 years.

R. K.

THE CYCLOPEDIA OF MEDICINE. VOL. 13. REVISION SERVICE. GEORGE MORRIS PIERSOL, B.S., M.D., Editor-in-Chief; EDWARD L. BORTZ, A.B., M.D., Assistant Editor. Chief Associate Editors: W. WAYNE BABCOCK, A.M., M.D., Surgery; CONRAD BERENS, M.D., Ophthalmology; P. BROOKE BLAND, M.D., Obstetrics and Gynecology; FRANCIS L. LEDERER, B.S., M.D., Otology, Laryngology and Rhinology; A. GRAEME MITCHELL, M.D., Pediatrics. Pp. 1063; 190 illustrations. Philadelphia: F. A. Davis Company, 1937. Price, \$12.00.

"To revise completely a work of the magnitude of the *Cyclopedia* frequently is obviously out of the question. Therefore . . . it is proposed to issue annually a service volume . . . which will keep the *Cyclopedia* thoroughly abreast of the times." In large part the book consists of abstracts of the literature which has appeared since the writing of the original articles. There are also a number of articles that obviously fill in gaps in the original publication. Although 117 authors have contributed to the present volume, there is very little duplication, a tribute to good editing. The material is well arranged and completely indexed.

R. K.

RECENT ADVANCES IN ENDOCRINOLOGY. By A. T. CAMERON, M.A., D.Sc. (EDIN.), F.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital. Pp. 458; 65 illustrations, including 3 plates. Third edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1936. Price, \$5.00.

In this edition there has been an increase from 365 to 458 pages, and a large increase in bibliography. Such an abstracting of the voluminous literature has value in permitting the reader to locate references on a given subject which he can consult in the original, and in giving a bird's-eye view of recent work in endocrines to one not actively working in this field. As the author himself undoubtedly realizes, it is not humanly possible for a person working in one field to be able to analyze critically the results in other special fields of endocrinology. The Reviewer would prefer to see less said about some published work that requires corroboration, but the author makes every attempt to be fair by referring to work on opposing sides of various subjects.

I. Z.

MODERN TREATMENT AND FORMULARY. By EDWARD A. MULLEN, P.D., M.D., F.A.C.S., Assistant Professor of Pharmacology and Physiology, Philadelphia College of Pharmacy and Science; Lieutenant-Commander, Medical Corps, U. S. Naval Reserves. Foreword by HORATIO C. WOOD, JR., Professor of Therapeutics in University of Pennsylvania, Graduate School of Medicine; Professor of Pharmacology and Physiology, Philadelphia College of Pharmacy and Science. Pp. 707. Philadelphia: F. A. Davis Company, 1936. Price, \$5.00.

THE author's goal was laudable: to place at the ready disposal of the busy practitioner the essentials of treatment as gleaned from standard works on therapeutics and current literature, with emphasis on the presentation of actual prescriptions—over 2000 of them. He has undoubtedly succeeded in bringing much that is useful to the attention of "a generation of physicians . . . not sufficiently grounded in *materia medica* . . ." He has however included much that is useless, perhaps even harmful, and there are a few important omissions. Thus there are 16 prescriptions for various combinations in which quinine may be employed in malaria, but no mention is made of plasmochin or atabrine. Prescriptions containing 8 or 9 ingredients smack of an unwarranted polypharmacy. Three grains of desiccated thyroid daily is hardly a proper prescription for neurasthenia,

without some reference to basal metabolism. There is no mention of etiologic agents (drugs) to be avoided in the treatment of patients with agranulocytic angina. Nothing is said of possible contraindications to quinidine. The author writes both English and metric dosages, but he thinks in terms of the English; else why write "menthol [972]?" A proprietary preparation with secret formula is recommended. If there is a more thorough winnowing of chaff from the wheat, this can be made a very useful book in its future editions.

R. K.

PATHOLOGY OF THE NERVOUS SYSTEM. A Student's Introduction. By J. HENRY BIGGART, M.D. (BELFAST). Pp. 335; 204 illustrations. Baltimore: William Wood & Co., 1936. Price, \$5.25.

THE recent appearance of several excellent texts on neuropathology reflects the present-day interest in neurology. The author's book, which he himself modestly terms "A Student's Introduction," is a clearly written and well-illustrated guide in which the principles of pathology are applied to the lesions of the nervous system. All too often in neuropathologic literature it has been apparent that the writers have not served their apprenticeship in the department of pathology. Specialization in a difficult field without adequate training has led to the invention of many meaningless terms for lesions in the nervous organs having their counterpart in well-known changes of other organs. Indeed, there has been a tendency to regard neuropathology as a subject of interest solely to the neurologist, and in many of our hospitals neuropathology has become divorced from general pathology. But, as Professor Drennan rightly says in his Foreword, "It will be unfortunate, however, if neuropathology is to lose contact with its parent, general pathology, for the same problems concern both. In this book the author has kept the relationship, and throughout there will be found analogies between the disease processes seen in the nervous tissue and in other tissues of the body. The apparent differences are shown to be due to the different anatomical factors—glial tissue in place of fibrous tissue, Virchow-Robin space for perivascular lymphatics, and so on." These sentences of Professor Drennan give so trenchantly the spirit of the author's text that the Reviewer has quoted them *verbatim*. It remains to say that the author has had a well-rounded training in pathologic laboratories in this country and Great Britain, and that this training is reflected in his admirable text, which is sincerely recommended not only to medical undergraduates, but to those professional pathologists who have slighted a most interesting field of their profession, and to practitioners who see and study the patient in the early stages of his disease.

B. L.

A TEXT-BOOK OF HISTOLOGY. Arranged upon an Embryological Basis. By J. LEWIS BREMER, M.D., Hersey Professor of Anatomy, Harvard University. Pp. 580; 455 illustrations (36 in colors). Fifth edition of "Lewis and Stohr." Philadelphia: P. Blakiston's Son & Co., Inc., 1936. Price, \$6.50.

"THE increasing vitality of the embryological and histological sciences within the last few years seems to require a rather radical revision of this textbook with the incorporation of much new material. More emphasis has been given to the normal functional changes in the various cells and to their activities in the living state, as correlated with the usual histological picture. The newer conceptions of the various hormones have been briefly included, and because of their importance the reaction on the endocrine glands has been advanced to a position ahead of the sections dealing with those organs in which their actions are best recognized. In general,

however, the book follows the same plan as in former editions, and emphasis is still laid more on development and the resulting form than on function, except as the latter helps to explain the morphology. . . . Some of the improved mechanical characteristics of this edition are—a large percentage of new illustrations, a glareless paper, a sturdy, cleanable and water resisting binding." (From Preface and Publishers' Statement.)

ALLERGIC DISEASES. THEIR DIAGNOSIS AND TREATMENT. By RAY M. BALLEAT, M.A., M.D., F.A.C.P., Associated Professor of Medicine and Lecturer on Diseases Due to Allergy, University of Oklahoma Medical School; Chief of the Allergy Clinic, University Hospital, etc. Assisted by RALPH BOWEN, B.A., M.D., F.A.A.P., Chief of Pediatric Section, Balleat Hay Fever and Asthma Clinic, Oklahoma City, Oklahoma. Pp. 516; 132 illustrations (8 in colors). Fourth edition, revised and enlarged. Philadelphia: F. A. Davis Company, 1936. Price, \$6.00.

ORIGINALLY planned as a manual for the instruction of patients, this book has been expanded in successive editions to serve also the general practitioner. It contains much practical information and advice, but the extensive use in asthma of endotracheal instillation of iodized oil, as recommended by the author, is to be condemned.

R. K.

METHODS OF TISSUE CULTURE IN VITRO. By RALPH BUCHSBAUM, Ph.D., Department of Zoölogy, University of Chicago, and *Outlines of Histological Methods, with Special Reference to Tissue Culture*, by CLAYTON G. LOOSLI, Ph.D., Department of Anatomy, University of Chicago. Pp. 81 (lithographed); 19 illustrations. Chicago: The University of Chicago Press, 1936. Price, \$1.00.

As stated in the Foreword, the booklet "presents a simplified method of tissue culture for a single investigator in an ordinary biological laboratory. All of the requirements for best growth have been included, but the attempt has been made to eliminate procedures of doubtful value, to minimize certain precautions which seem to be overemphasized by some workers, and to recommend equipment which is as inexpensive as possible." In addition, there is given an outline of methods for fixing, embedding, sectioning and staining cultures and control tissues.

The authors have presented their subject with clearness and admirable brevity. The illustrations and the references to books and articles on technique are well chosen. The beginner will find in this book a guide that will encourage rather than scare him.

B. L.

A PREFACE TO NERVOUS DISEASES. By STANLEY COBB, A.B., M.D., Bullard Professor of Neuropathology, Harvard Medical School; Psychiatrist-in-Chief, Massachusetts General Hospital. Pp. 173; 13 illustrations. Baltimore: William Wood & Co., 1936. Price, \$2.50.

His long teaching experience has led the author to views expressed in the Foreword: "To make the student understand the important principles, the teacher must simplify and schematize; frankly, of course. The anatomy and physiology of the brain must be taught with the pathology. In the curriculum each may be put into a separate compartment. To the intellect they are inseparable.

"The book is written to give to students of medicine (and all good physicians remain students as long as they live) the facts and correlations needed to understand the simpler workings of the central nervous system. In truth, little more than these simple mechanisms is thoroughly understood, and even some of these are still controversial. Thus, adherence to prin-

ciples that are fairly well established has kept the book small, for it has been my aim to mention only those anatomical structures the physiology of which is known, to discuss only physiological processes for which there is at least a fairly well-substantiated anatomical correlation, and to describe only the pathology that has fundamental significance. References are given for the reader who would study details. The book is a preface, to start the student with a three-dimensional orientation towards neurology and psychiatry—a brief, concurrent anatomy, physiology, and pathology.”

The book is divided into 12 short chapters: Autonomic nervous system; segmental and suprasegmental aspects of the cerebrospinal nervous system; motor integration and locomotion; functional localization in the cerebral cortex; consciousness and the “mind-body” problem; cerebral circulation; cerebrospinal fluid; paths of infection to the nervous system; general histologic pathology; the peripheral nerve and neuritis; special histologic pathology; epilepsy and the psychoses.

The author has succeeded in welding together the principles of neurology which he presents in a clear and pleasant style. B. L.

MRS. EDDY PURLOINS FROM HEGEL. Newly Discovered Source Reveals Amazing Plagiarisms in Science and Health. By WALTER M. HAUSHALTER. Pp. 126; illustrated. Boston: A. A. Beauchamp, 1936. Price, \$1.50.

In 1907 Mark Twain strongly stated his belief that Mrs. Eddy was not the sole author of “Science and Health,” suggesting that parts of it were obviously the product of an intellect far greater than that displayed by Mrs. Eddy in other writings, indubitably hers. As the author points out, Twain’s “surmise was in the direction of some unknown author who died before his work gained the light of public attention.” In proof of this the author offers a photostatic copy of a manuscript which recently came to his hands in the course of his search for Mrs. Eddy’s possible source material. Entitled “The Metaphysical Religion of Hegel,” it bears the name of Francis Lieber, distinguished German-American publicist, by whom it was sent in 1866 to Hiram Crafts. In Crafts’ home Mrs. Eddy lived from 1866 to 1868 and there, according to a biographer, “she began to systematize her ideas and write out a new manuscript.” “Science and Health” was not published until 1875, three years after Lieber’s death. Numerous quotations would show that the Lieber manuscript is the chief source from which she drew what she could grasp of Hegel’s transcendental philosophy, and from which she appears to have plagiarized most brazenly. It is to be hoped that the author will bring forward further evidence fully to authenticate his extremely interesting and important find.

R. K.

THE HARVEY LECTURES. SERIES XXXI. Delivered under the Auspices of The Harvey Society of New York, 1935–1936. Under the patronage of The New York Academy of Medicine. Pp. 255; illustrated. Baltimore: The Williams & Wilkins Company, 1936. Price, \$4.00.

Of the 8 lectures of last year’s series, the first is by Max Bergmann on “Proteins and Proteolytic Enzymes.” He points out the importance of a complicated periodic repetition of simple structural elements, as a concept of protein structure and the promise that study of proteolytic enzymes and selective precipitation gives for elucidation of the structure of the proteins. In the second lecture, “The Significance of Chimpanzee-Culture for Biological Research,” Yerkes defends the thesis “that experimental biology requires and should demand, as does chemistry, relatively standardized, describable, and carefully controlled materials of research.” Rous’ “Virus Tumors and the Tumor Problem” describes the virus tumors

of fowl and rabbits—Lucké's renal carcinoma of frogs is not considered. Rous combats 8 difficulties that "stand in the way of the supposition, for experimental purposes, that the general run of malignant growths is due to viruses." In the fourth lecture, "Relations Between the Parathyroids, the Hypophysis and the Pancreas," Houssay presents a number of these complicated relationships. J. F. Fulton's lecture on "Interrelation of Cerebrum and Cerebellum in the Regulation of Somatic and Autonomic Functions," the longest of the series, relates how the results, especially of decerebellation and decortication, demonstrate "the coëxistence in the same anatomical area of the cortex, as well as in the cerebellum, of autonomic and of somatic representation (which) makes possible simultaneous and appropriate adjustments." Shope's discussion of "The Influenzas of Swine and Man," presents the highly important demonstration that swine influenza is due to the concerted action of a filtrable virus and a bacterium and emphasizes similarities in the etiology of swine and human influenza. Warren Lewis' study of "Malignant Cells" in tissue cultures (especially with the roller-tube technique) supports the view that they are permanently altered cells, cytologically and physiologically. The last lecture of the series, "The Physiology of the Bronchial Vascular System," by I. de Burgh Daly, of the University of Edinburgh, describes work elucidating the importance of the bronchial vascular system in the maintenance of intrinsic pulmonary nervous mechanisms.

"The high standard of these famous lectures has been well maintained," has long since become a truism; yet it is the most fitting comment that one can make on this volume.

E. K.

HUGH OWEN THOMAS. *A Personal Study*. By FREDERICK WATSON. Pp. 94; illustrated. New York: Oxford University Press, 1934. Price, \$4.25.

HUGH OWEN THOMAS. *His Principles and Practice*. By D. McCRAE AITKEN, M.A., M.B., CH.B. (ED.), F.R.C.S. (ED. AND ENG.), Director of Surgery, Robert Jones and Agnew Hunt Orthopædic Hospital; Senior Surgeon, St. Vincent's Orthopædic Hospital, etc. Pp. 96; 1 illustration, 8 plates. New York: Oxford University Press, 1935. Price, \$4.25.

THESE two monographs dealing with the life and work of Thomas were prepared as companion books. "The Personal Study" was written by Thomas' son-in-law; the "Principles and Practice" by a pupil and colleague of Sir Robert Jones who in turn was a brother-in-law to Thomas. Both works were inspired by Sir Robert. It had been his hope to issue in 1934 a centenary volume dealing with epochal work in orthopedics of his famed friend and relative. The death in 1933 of Sir Robert made it necessary that the work be done by others. The choice of authors and the division of their labors was a most happy one. To Hugh Thomas orthopedic surgery throughout the world owes much. To it Thomas brought the skilled hands of a master craftsman and a mind that insisted upon the application of physiology to the treatment of deformities. The results of such a happy conjunction of talents could only be the rational solution of the problems attacked. When we learn of the personal characteristics of the man, it is easy to see how his principles and practices gained widespread circulation. No other man so advanced the mechanical and manipulative phases of orthopedic surgery as did Hugh Owen Thomas. Few workers since have been able to extend the domain of these branches. It is most interesting to realize that the great advance in the operative field of orthopedic surgery was given its impetus by Thomas' brother-in-law, Sir Robert Jones. These two monographs are of great interest and value. They are splendidly written and well illustrated.

G. W.

PRINCIPLES OF BACTERIOLOGY. By ARTHUR A. EISENBERG, A.B., M.D., Director of Laboratories, Sydenham Hospital New York, and MABEL F. HUNTLY, R.N., M.A., Director of Nursing, Wesson Memorial Hospital, Springfield, Mass. With annotations and a Section on Microbic Variations by F. E. COLLEN, M.S., Ph.D., Professor of Bacteriology, Vocational School, Milwaukee. Pp. 378; 90 illustrations, 8 colored plates. Sixth edition. St. Louis: The C. V. Mosby Company, 1935. Price, \$2.75.

THIS useful introduction to bacteriology has been improved by the revision of several sections, especially those dealing with the leukocytes, with sensitivity phenomena and with diseases due to animal parasites. Except for instances in which the effect to obtain simplicity of diction has resulted in loss of accuracy, the book achieves its purpose. The section devoted to study of specific disease agents is properly subordinate; but the grouping of species by physiologic effects rather than by biologic relationships is likely to result in confusion, if a systemic laboratory study course accompanies the didactic work. J. F.

APPLIED DIETETICS. For Adults and Children in Health and Disease. By SANFORD BLUM, A.B., M.S., M.D., Head of Department of Pediatrics, and Director of Research Laboratory, San Francisco Polyclinic and Post-Graduate School. Pp. 408. Philadelphia: F. A. Davis Company, 1936. Price, \$4.75.

WHILE the book contains much that is good and practical, especially in the section on the dietary for infants and children, it also contains much that is questionable and irrational. Thus it is advised that the normal adult male shall avoid preserved, salted, spiced and canned meats and fish; tongue, kidneys, sausage, liver, pot roast, stews, pork, duck, goose, soup meat, hash; herring, lobsters, crabs, clams, mussels; berries, jams, preserves, etc. There is little attention paid to quantities of foods. The book is not recommended. R. K.

THE BRITISH ENCYCLOPÆDIA OF MEDICAL PRACTICE. Including Medicine, Surgery, Obstetrics, Gynæcology, and other Special Subjects. Vol. 1, Abdominal Pain to Appendicitis; Vol. 2, Apraxia to Carriers in Infective Disease. Under the General Editorship of SIR HUMPHRY ROLLESTON, Bt., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of the Royal College of Physicians of London. With the assistance in a consultative capacity of F. R. FRASER, M.D., F.R.C.P., Professor of Medicine, University of London; G. GREY TURNER, M.S., D.Ch., F.R.C.S., Professor of Surgery, University of London; JAMES YOUNG, D.S.O., M.D., F.R.C.S.E., F.C.O.G., Professor of Obstetrics and Gynæcology, University of London; SIR LEONARD ROGERS, K.C.S.I., LL.D., F.R.C.P., F.R.C.S., F.R.S., Extra Physician, Hospital for Tropical Disease, London; F. M. R. WALSH, O.B.E., M.D., F.R.C.P., Fellow, University College. Pp.: Vol. 1, 802; Vol. 2, 830. Illustrations: Vol. 1, 96; Vol. 2, 111, and 15 plates (5 in colors). London: Butterworth & Co. (Publishers), Ltd., 1936. Price, \$12.00 per volume.

A PRODUCTION of this size by such distinguished contributors and eminent editors is almost necessarily an event of prime importance in the medical book publishing world. The fortunate owners of these volumes will have authoritative statements on the whole field of medical practice, including medicine, surgery, obstetrics, gynæcology and other specialties. This in itself makes possession of such a work as necessary as access to the Encyclopædia Britannica is to any cultured individual. An added and important

benefit will be the "Keyed Supplementary" volumes which will keep the work regularly up to date. "Arranged for the convenience of the busy practitioner," the encyclopedia frankly concentrates on diagnosis and treatment, minimizing historical data and including only those pathologic details that are essential for practical purposes. The first volume contains 51 articles by 46 authors; the second, 56 articles by 62 authors. They vary in length from a single page (Ainhum, Angio-keratoma, Bornholm Disease) to whole treatises, such as the 64 pages on Anemia. The more important articles in these 2 volumes are on Acute Abdominal Emergencies, Abortion, Accessory Sinuses of the Nose, Adiposity, Adrenal Gland Diseases, Allergy, Amputation, Anæmia, Anæsthesia, Aneurysm, Angina Pectoris and Coronary Thrombosis, Anus Diseases, Arterial Disease and Degeneration, Arthritis, Backache and Lumbago, Bladder Diseases, Blood Examination, Brain Tumour, Breast Diseases. Ease of reference has been stressed throughout; the exhaustive 60-page index gives many cross-references that greatly increase the encyclopedic value of each volume as it appears. Thus while "acidosis" is covered in a 7-page article, its relation to adenoids, alcoholism, alkalosis, anesthesia and so on can readily be found in other parts of the volume by reference to the index.

The recent appearance of the new edition of Sajous' 12-volume Cyclopedia in this country inevitably invites comparisons with this great work, though as the two productions have been developed along somewhat different lines the overlap is far from complete. In general, one may say that the American work has more articles that tend to be shorter in length, though some (*e. g.*, adrenal gland, appendicitis) are as long as the longest of the English, and the extra 3 volumes have apparently permitted many to be longer than those on the same subject in the English work. One feature that might well be copied in later volumes of the work under review is the inclusion in smaller print of matter that is necessary but of minor importance. In regard to the topics considered, anyone, of course, can criticize the omission of this or that subject (*e. g.*, abscess, acetanilid, acetone) or disproportions of allotted space (*e. g.*, 4 pages for "ackee poisoning" *vs.* 5 for amyloid disease, which by the way does not appear at all in the American work); but how can even substantial agreement be expected in such a task? Furthermore, subjects missed in A and B may turn up under a different classification in later volumes. The task of selection of topics for treatment must indeed be about the most difficult of all in the preparation of such a work. For American readers the all-British authorship (one might almost say the all-London) gives the added interest of a transatlantic presentation that nevertheless can be assimilated without confusion by those differently trained on this side. Of course, most important of all in any scientific work, is the value of the contributions themselves; also, of course, no one reader can estimate this value even after long acquaintance. Time and a multitude of readers will have to supply the verdict. However, the Reviewer believes that if the remaining volumes of the set live up to the promise of the first 2, this will indeed be a valuable addition to medical literature.

E. K.

DIFFERENTIALDIAGNOSE IN DER INNEREN MEDIZIN. LIEFERUNG 2. 1.-6. TAUSEND. By PROF. DR. MED. O. NAEGELI, Direktor der Medizinischen Universitätsklinik, Zürich. Pp. 414; 97 illustrations. Leipzig: Georg Thieme, 1936. Price, Rm. 9.60.

THE second "Lieferung" of this work treats, in systematic manner the, differential diagnosis of diseases of the abdomen, lung and pleura. The first of these—the longest section—deals briefly with such matters as abdominal pains of various kinds, hemorrhage and anemia, resistance, stenoses, ileus, gastric ulcer, carcinoma, gastritis, gastroduodenal symptoms, appendicitis, peritonitis and so on.

E. K.

A HEALTH EDUCATION WORKBOOK. For Teachers, Parents, Nurses and Social Workers. By KATHLEEN WILKINSON WOOTTEN, M.A., Professor of Health; Head, Department of Health and Physical Education, Georgia State Teachers College for Women, Milledgeville, Georgia. Pp. 273. New York: A. S. Barnes & Co., Inc., 1936. Price, \$1.50, paper binding.

THIS outline for health education is best suited for the grade school teacher, and the athletic instructor who is frequently required to supervise health education. The book is too elementary for college teachers. In addition to the usual hygiene subjects, as diet, exercise, and sex, the qualifications for a health teacher are outlined, and a method of presentation of health education is given. There is very little mention of public health work, and nothing on the history of medicine—both of which are necessary for a complete education on health. There are many quotations from health writers that are well adapted for pedagogical work. The subject matter in each chapter is presented as: "Objectives," "Study Outline," "Activities," and lastly, "References." There are many good references for the lay reader.

As a skeleton outline for elementary health education and school health supervision by a layman, this book will find a place. N. B.

SYNOPSIS OF ANO-RECTAL DISEASES. By LOUIS J. HIRSCHMAN, M.D., F.A.C.S., Ex-Vice-President, A.M.A., Professor of Proctology, Wayne University, etc. Pp. 288; 174 illustrations and 6 color plates. St. Louis: The C. V. Mosby Company, 1937. Price, \$3.50.

DR. HIRSCHMAN has already favored both students and practitioners with 4 editions of his Handbook on Diseases of the Anus and Rectum. The synopsis now presented affords the reader the summary of a lifetime of experience in this field. As pointed out in the preface, the book is subject to the limitations of a synopsis. However, the concise arrangement of subject matter, the frequent use of apt illustrations and the omission of controversial minutiae will undoubtedly make it very valuable to the large group of physicians for whom it was written. I. R.

ANIMAL MICROLOGY. Practical Exercises in Zoölogical Micro-technique. By MICHAEL F. GUYER, Professor of Zoölogy in the University of Wisconsin. With a chapter on Drawing by ELIZABETH A. (SMITH) BEAN, Former Assistant Professor in Zoölogy in the University of Wisconsin. Pp. 331; 76 illustrations. Fourth edition, revised. Chicago: The University of Chicago Press, 1936. Price, \$2.50.

THE fourth edition of this book follows the general pattern of earlier ones. It omits discussions of how and why various methods were developed, and its make up is confused. For example, on page 5, "keep everything clean!" heads "important general rules," but cleaning solutions are mentioned first on page 61 and only in connection with used slides. Revision of other chapters seems indicated also; that on the paraffin method is inadequate; the microtome as a machine is scarcely mentioned and newer apparatus for sharpening knives is not discussed. Frozen section technique seems out of place in a book which deals chiefly with the subject matter of elementary zoölogy. This edition includes a chapter on the use of "dioxan" (diethylene oxide) in histological technique. This and outlines of numerous standard methods will make it useful for experienced technicians; but, for those who wish more adequate information on histologic methods, other books will be more satisfactory. H. R.

NEW BOOKS.

Clinical Laboratory Diagnosis. By SAMUEL A. LEVINSON, M.S., M.D., Director of Laboratories, Research and Educational Hospitals, Chicago; Associate Professor of Pathology and Bacteriology and Assistant Professor of Medicine, University of Illinois College of Medicine; and ROBERT P. MACFATE, CH.E., M.S., Assistant Director of Laboratories, Research and Educational Hospitals, Chicago; Associate in Pathology and Bacteriology and Instructor of Physiological Chemistry, University of Illinois College of Medicine. Pp. 877; 144 illustrations, 78 tables and 13 plates (5 in colors). Philadelphia: Lea & Febiger, 1937. Price, \$9.50.

Das Hormon des Corpus Luteum. (Biologie, Chemie und Klinik.) By DR. ERICH FELS, Dozent für Geburtshilfe und Gynäkologie, Leiter der Abteilung für Biologie und experimentelle Chirurgie am Instituto de Maternidad de la Sociedad de Beneficencia, Buenos Aires. Pp. 169; 40 illustrations. Leipzig: Franz Deuticke, 1937. Price, Paper, M. 12; Bound, M. 14.40.

Le Artropatie Croniche. Escluse Quelle da Germi Conosciuti. (In Monografia Medico-Chirurgiche d'Attualita.) By DOTT GAETANO ZAPPALA, degli Ospedali Riuniti di Roma. Collaborazione del PROF. GIUSEPPE LAZZARO. Prefazione del PROF. CESARE ANTONUCCI, Chirurgo Primario degli Ospedali Riuniti di Roma. Pp. 237; 9 illustrations. Roma: Luigi Pozzi, 1936.

This attempt to present "the actual state of our knowledge of chronic arthritis" appears to suffer from lack of acquaintance with the English speaking literature on the subject.

Fisiopatologia del simpatico nell'uomo. Memoria premiata dal R. Istituto Lombardo di Scienze e Lettere con il premio di fondazione Fossati. (In Monografie Medico-Chirurgiche d'Attualita.) By PROF. GINO PIERU, Chirurgo Primario nell'Ospedale Civile di Udine. Prefazione del PROF. CESARE FRUGONI, Direttore della Clinica Medica della R. Università di Roma. Pp. 78; 41 illustrations. Roma: Luigi Pozzi, 1936.

This essay, which was the prize of the Fossatti Foundation of the Royal Institute of Science and Literature of Lombardy, is based on a study of disorders regarded as due to sympathetic stimulation or paralysis.

Electrical Signs of Nervous Activity. (The Eldridge Reeves Johnson Foundation for Medical Physics.) By JOSEPH ERLANGER, Professor of Physiology, Washington University, and HERBERT S. GASSER, Director, The Rockefeller Institute for Medical Research. Pp. 221; 113 illustrations. Philadelphia: University of Pennsylvania Press; London: Humphrey Milford; Oxford University Press, 1937. Price, \$3.50.

The Psychology of Eating. By LEWIS ROBERT WOLBERG, M.D. Pp. 321. New York: Robert M. McBride & Co., 1936. Price, \$3.00.

The Medical Clinics of North America, Vol. 21, No. 2 (Boston Number—March, 1937). Pp. 642; illustrated. Philadelphia: W. B. Saunders Company, 1937.

The Ocular Fundus in Diagnosis and Treatment. By DONALD T. ATKINSON, M.D., F.A.C.S., Consulting Ophthalmologist to the Santa Rosa Infirmary and the Nix Hospital, San Antonio, Texas, etc. Pp. 142; 48 illustrations and 58 colored plates. Philadelphia: Lea & Febiger, 1937. Price, \$10.00.

Cancer and Diet. With Facts and Observations on Related Subjects. By FREDERICK L. HOFFMAN, LL.D., The Biochemical Research Foundation of the Franklin Institute, Philadelphia, Pa. Pp. 767; 187 tables. Baltimore: The Williams & Wilkins Company, 1937. Price, \$5.00.

Cataract. Its Preventive and Medical Treatment. For Specialists, General Practitioners and Students. By A. EDWARD DAVIS, A.M., M.D., Formerly Professor of Ophthalmology, New York Post-Graduate Medical School and Hospital (Columbia University), etc. Pp. 161; 11 charts. Philadelphia: F. A. Davis Company, 1937. Price, \$3.00.

Compulsory Health Insurance and Disease Control. By FREDERICK L. HOFFMAN, LL.D., Consulting Statistician, Philadelphia, Pa. Pp. 38. New York: Public Relations Bureau, Medical Society of the State of New York, 1936. Price, 10 cents.

This is a comparison of vital statistics in the United States with those of several foreign countries in which health insurance has been in operation for many years. It is not favorable to health insurance.

The History of the Acute Exanthemata. The Fitzpatrick Lectures for 1935 and 1936. Delivered before the Royal College of Physicians of London. By J. D. ROLLESTON, M.A., M.D., F.R.C.P., F.S.A., Medical Superintendent, Western Fever Hospital, London. Pp. 114; illustrated. London: William Heinemann (Medical Books), Ltd., 1937. Price, 7s. 6d.

Diabetes. A Modern Manual. By ANTHONY M. SINDONI, JR., M.D., Chief of the Diseases of Metabolism at the St. Agnes Hospital; Chief Consultant in the Diseases of Metabolism at the Oncologic Hospital, etc. Introduction by MORRIS FISHBEIN, M.D., Editor, *Journal of the American Medical Association*, with a Foreword by GEORGE MORRIS PIERSON, B.S., M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania; Physician to the Graduate School Hospital, etc. Pp. 240. New York: McGraw-Hill Book Company, Inc., 1937. Price, \$2.00.

Christian R. Holmes. Man and Physician. By MARTIN FISCHER. Pp. 233; illustrated. Springfield, Ill.: Charles C Thomas, 1937. Price, \$4.00.

Handbook of Orthopædic Surgery. By ALFRED RIVES SHANDS, JR., B.A., M.D., Associate Professor of Surgery in Charge of Orthopædic Surgery, Duke University School of Medicine, and Chief of the Orthopædic Service, Duke Hospital, Durham, N. C., etc. In collaboration with RICHARD BEVERLY RANEY, B.A., M.D., Instructor in Orthopædic Surgery, Duke University School of Medicine. Pp. 593; 169 illustrations. St. Louis: The C. V. Mosby Company, 1937. Price, \$5.00.

NEW EDITIONS.

The Operations of Surgery, Vol. II. The Abdomen. By R. P. ROWLANDS, M.S. (LOND.), F.R.C.S. (ENG.), Late Surgeon to Guy's Hospital; Late Lecturer on Surgery to the Medical School; and PHILIP TURNER, B.Sc., M.S. (LOND.), F.R.C.S. (ENG.), Consulting Surgeon to Guy's Hospital; Formerly Lecturer on Surgery and Teacher of Operative Surgery to the Medical School. Pp. 998; 514 illustrations (4 in color). Eighth edition. Baltimore: William Wood & Co., 1937. Price, \$10.00.

The Chemistry of Natural Products Related to Phenanthrene. By L. F. FIESER, Associate Professor of Chemistry, Harvard University. Pp. 456. Second Edition with an Appendix. New York: Reinhold Publishing Corporation, 1937. Price, \$7.00.

Medical Greek and Latin at a Glance. By WALTER R. AGARD, B.LITT. (OXON.), Professor of Greek, University of Wisconsin. With an Introduction by C. H. BUNTING, M.D., Professor of Pathology, University of Wisconsin. Pp. 87 (every other page blank). Second Edition revised. New York: Paul B. Hoeber, Inc., 1937. Price, \$1.50.

PROGRESS OF MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF

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OXYGEN THERAPY.*

OXYGEN treatment is an example of a therapeutic procedure long recognized in principle yet only recently shown to have practical applicability and significance. The biologic significance of oxygen was recognized by Lavoisier in the same year that it was discovered by Priestley⁴⁵. His epoch-making experiments, begun in 1775 and ending with the guillotine in 1794, demonstrated that oxygen is absorbed through the lungs and that it plays a similar rôle in the oxidative process of living as in that of non-living systems.³⁴ Priestley himself recognized the therapeutic possibilities of oxygen in asphyxial conditions.⁴⁵ As early as 1798, Thomas Beddoes founded a Pneumatic Institute in Clifton, where oxygen was used in the treatment of asthma and heart disease and also of opium poisoning.³⁹ Others have advocated its use in a variety of conditions, including tuberculosis, diabetes, syphilis, gout and hysteria. Because of its indiscriminate application, oxygen therapy fell into disuse. Its rational use became established only after physiologic and clinical investigations had discovered the nature of certain normal and morbid bodily states, particularly the various types of anoxia. When methods were finally devised which made possible the measurement of changes following its administration, and when industrial development made its prolonged administration

* This discussion makes no attempt to review the subject completely. Comprehensive discussions, particularly on the physiologic principles of the subject, may be found in the following works: (a) Pagel, J.: *Handb. d. Sauerstoff-therapie*, ed. by M. Michaelis, Berlin, 1906; (b) Lundsgaard, Ch., and Van Slyke, D.D.: *Cyanosis*, *Medicine*, 2, 1, 1923; (c) Meakins, J. C., and Davies, H. W.: *Respiratory Function in Disease*, London, Oliver & Boyd, 1925; (d) Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, The Williams & Wilkins Company, Baltimore, 1931. Chap. XII, Hemoglobin and Oxygen, 1, 518.

practical, comfortable and reasonably economical, oxygen became an important therapeutic agent. This has been accomplished, to a large extent, during the past two decades.

In the evaluation of the therapeutic usefulness of oxygen two questions must be answered: 1, Is oxygen of value only as a substitute in conditions in which anoxia of tissues exists? 2, Is it also beneficial in conditions in which there is a normal supply of oxygen?

Oxygen Deficiency. The manifestations of oxygen deficiency have been established primarily by studies on the effects of gas mixtures with reduced oxygen concentration, particularly by Haldane^{27a} and Barcroft,⁸ and by studies on the effect of reduced atmospheric pressure under artificial conditions, as in chambers,²⁵ and at high altitudes.²² The manifestations of these different types of oxygen deficiency are essentially the same and they depend mainly on whether the anoxia is acute or chronic.

There is scarcely any storage of oxygen in the body. The slight storage in the lungs is evidenced by the fact that few can hold their respiration more than 2 minutes. If, therefore, air is washed out of the lungs by inert gases, unconsciousness may ensue almost at once. Thus, a miner who walks into a pocket of methane "is struck down as though he had been felled by a blow on the head."⁴⁰ Gradual deprivation of oxygen produces impairment of mental function, usually without appreciation of this fact by the subject. There is an increase in the rate and, to a lesser extent, in the depth of respiration. The normal range of the Hering-Brauer reflex is diminished. The heart rate is increased and the pulse is feeble. Cyanosis, vertigo, anorexia, nausea and vomiting, diarrhea, muscular fatigue and headaches are the most common symptoms of prolonged oxygen want. 'Later Cheyne-Stokes' respiration and a fall in arterial pressure, often preceded by a rise, may occur. The heart may become dilated. As terminal signs, hallucinations, circulatory collapse, unconsciousness and coma may occur.^{7,25,27b} It has recently been pointed out that many of these manifestations depend primarily on anoxia of the central nervous system and that similar symptoms occur with the onset of other types of collapse.⁵⁸ Prolonged oxygen lack may produce changes within the body and particularly in the nervous system, associated with a tendency to irreversible processes.⁵⁹

Susceptibility to oxygen lack varies greatly among individuals.²¹ Activity of reflexes can influence considerably such sensitivity of the organism. Selladurai and Wright⁵¹ have shown experimentally that oxygen lack acts as a stimulant to the respiration through the vagi and the sinus nerves. The integrity of the "buffer nerves" may enable the respiratory center to withstand for long periods degrees of anoxemia which are lethal to it when it has been isolated by section of the vagi and denervation of the sinuses. In a recent study on the mode of action of oxygen lack on respiration Wright has demonstrated⁵² that anoxia stimulates respiration only when the sino-aortic nerves are intact. The respiratory center of animals with denervated carotid sinuses and aortic arch (*i. e.*, vasosensory zones) fails when there is approximately twice as much oxygen in the blood as is lethal to the normally innervated center. Thus intact animals can breathe for long periods a concentration of oxygen as low as 4%, while "denervated

animals" have often failed in an atmosphere containing 13 or even 14% of oxygen. It is suggested that afferent impulses along the carotid sinus and aortic afferent nerves can antagonize to some extent the direct chemical changes produced in the respiratory center by anoxia. That other factors can also influence the susceptibility of the body to oxygen want has been claimed by the Asher school.^{1,2} Variations in these physiologic factors may well bear on certain conditions observed in the clinic.

Barcroft⁶ has classified oxygen deficiencies as follows: 1, anoxemic type, characterized by interference in the respiratory exchange of oxygen within the lungs; 2, stagnant type, due to a disturbance of the circulation in which oxygen is utilized more rapidly than it is supplied; 3, anemic type, associated with lowered capacity of the blood to carry oxygen and with secondary low oxygen tension of the blood. A fourth type of anoxemia, the "histotoxic" type, in which the cells themselves have difficulty in utilizing the available oxygen (as in cyanide poisoning) has been added.⁴²

Effects of Oxygen on Subjects Without Oxygen Deficiency. As early as 1789 Lavoisier and Sequin²³ discovered that administration of oxygen had no effect in increasing metabolism. This finding has been amply confirmed.^{24,43,46} In concentrations up to about 70 to 80%, oxygen does not seem to exert toxic effects. The prolonged use of higher concentrations or of pure oxygen is "irritant" to the lungs and poisonous to the central nervous system;⁴⁰ the degree and nature of the toxic effect, however, is not well understood.¹¹ It has been claimed that increased tissue acidity due to carbon dioxide retention is a factor in the production of the convulsions occurring in oxygen poisoning.^{10,18a,26} This explanation, however, has been questioned recently.¹¹ Behnke, Johnson, Poppen and Motley¹¹ have demonstrated that the response of healthy subjects to inhalation of pure oxygen at normal and at increased atmospheric pressure is variable. Healthy men between the ages of 22 and 40 can breathe pure oxygen with comparative safety for 4 hours under normal atmospheric conditions, for 3 hours at 2 atmospheric pressure and for 2 hours at 3 atmospheric pressure. At 4 atmospheric pressure transient syncope with fall in blood pressure was observed and in one subject generalized convulsions developed after 45 minutes. It is of interest that at 4 atmospheric pressures the physically absorbed oxygen is about 7 vols. %, a concentration sufficient to satisfy the tissue requirement. At this pressure, however, striking effects of oxygen are observed.¹² In animals, first convulsions and then paralysis of the respiration has been described.⁵²

When oxygen is inhaled in high concentrations the only physiologic change detectable before the appearance of the toxic effects on the nervous system is the lowered cardiac rate. This effect, together with an increase in arterial saturation from 95 to 100% and an increase in physical absorption, may be the source of some therapeutic benefit following oxygen administration in cases without anoxia. It is doubtful, however, whether these responses are of practical therapeutic significance. The blood pressure is not altered. There is no definite effect on the cardiac output, as both slight increases and decreases have been reported.^{29,33}

Effect of Oxygen in the Presence of Oxygen Want. Oxygen therapy is, obviously, particularly indicated in diseases associated with oxygen lack. A consideration of the various types of anoxias indicates that the anoxemic type, associated with reduced arterial oxygen saturation, is the only type in which oxygen may be of striking benefit. In the stagnant, anemic and histotoxic types, the arterial oxygen saturation is normal and hence oxygen can, at best, be of little value.^{14,31} It has been claimed, on the other hand, that in healthy subjects increase of lactic acid in the blood and its elimination in the urine after strenuous muscular exercise can be influenced by the inhalation of oxygen.³⁰ This would suggest that the problem of oxygen therapy in the anoxias without anoxemia is not settled.

Oxygen therapy does not benefit every type of arterial anoxemic anoxia. The theoretical principle of oxygen therapy is that an increased concentration of oxygen raises, relatively or absolutely, the partial pressure of the alveolar oxygen. By the administration of oxygen a normal or an elevated alveolar oxygen pressure can thus be produced in conditions in which a low alveolar oxygen pressure exists as a result of changes in the environmental air (asphyxial conditions), in the air passages (strictures, emphysema, etc.) or in the ventilation (shallow breathing). In instances in which anoxemia is the result of changes in the alveolar wall (*i. e.*, decreased permeability) a high oxygen concentration elevates the partial pressure of the alveolar oxygen and increases its diffusion into the blood within the pulmonary capillaries. In view of the fact that the time factor also enters into the adequate oxygenation of the blood in the lungs, a rapid pulmonary flow may, theoretically at least, be responsible for anoxemia. Oxygen therapy will therefore accelerate the entrance of oxygen into the blood and so compensate for the rapidity of the blood flow.³¹ In each of these 3 forms of arterial anoxemia oxygen enhances the force which drives oxygen into the arterial blood. If, on the other hand, anoxemia results from such a gross distortion of any of these forms that even the increased oxygen atmosphere is inadequate, or if the anoxemia results from cardiac shunts, oxygen may be without benefit even in the anoxemic type of anoxia. These considerations clearly indicate the diseases in which oxygen therapy may be of benefit. In the anoxemic type of anoxia improvement will manifest itself mainly in: 1, disappearance of cyanosis; 2, disappearance of cerebral symptoms; 3, improved function of the vegetative centers; 4, lowered cardiac rate; 5, improved myocardial functions; 6, improved capillary permeability.

The *value of oxygen therapy* in anoxemic anoxia is distinct, though the degree of benefit is difficult to estimate. A statistical analysis fails to disclose a lowered mortality rate in treated groups of patients^{3a,b,17b}; it is questionable, however, whether oxygen therapy lends itself to such statistical analysis. The therapeutic value of oxygen is based on theoretical consideration, as already indicated; on the disappearance of arterial anoxemia following its administration;^{13b} and, finally, on the disappearance and reappearance of symptoms following administration and withdrawal, respectively, of high concentrations of oxygen.²

Methods of Administration. Oxygen has been administered by inhalation, subcutaneous and percutaneous methods. The *inhalation method* is the only rational, practical method in use today. It is gener-

ally agreed that the concentration of the oxygen mixture administered should be from 35 to 60%.¹⁴ Oxygen is administered in chambers and through tents, boxes, catheters and masks. Each method has advantages and disadvantages. The *oxygen chamber*^{19,55} represents the most comfortable and normal method. Its disadvantage is the expense of construction and of operation, since it requires a special nursing staff. The *tent method* is widely applied. There are many types in use. It is essential that operation of the tent should be noiseless, that the circulation of air should be free, and that the humidity and carbon dioxide should be controlled. There should also be a wide range of ventilation without change in the oxygen concentration. The tent should be capacious and well supplied with windows^{3a,b,d,14} and should have a wall which is not easily permeable to oxygen.³⁶ The concentrations of oxygen, carbon dioxide and humidity should be tested routinely 3 times a day. The concentration of oxygen should be between 35 and 60%, depending on the condition of the patient. An initial flow of about 15 liters a minute for 20 minutes, followed by a continuous inflow of from 7 to 8 liters a minute, is the usual procedure. The average cost of operation, including oxygen and ice, is \$6.00 a day. Modern, improved tents can be used without a special nursing staff. A simple and practical "oxygen box" for use in the treatment of babies has been described by Burgess and Burgess.^{15,16}

Recent studies^{9,37,44,59} have demonstrated that the administration of oxygen through a *nasal catheter* is efficacious and practical. This method involves a simple technique and is economical. The patient can be nursed without difficulty and the treatment can be administered if he is delirious. Among 31 patients requiring continuous oxygen therapy, Porter⁴⁴ found only one who could not tolerate this method of administration. He advocates the following technique: A rubber catheter, size 10 to 14 F. fenestrated near the tip, is introduced through the naris into the oral pharynx far enough so that it may be well discerned behind the soft palate. It is then withdrawn until almost out of sight and is strapped with adhesive tape. Twice daily the catheter should be withdrawn for the purpose of cleaning and another inserted. A mild nasal oil not only facilitates the introduction, but also adds to the comfort of the patient. In delirious patients it is advisable to introduce the new catheter through the opposite nostril and to strap it well before removing the old one. Marriott and Robson³⁷ have recently found that with an oxygen flow of from 4 to 16 liters a minute the alveolar oxygen concentration varied between 29 and 58%. With the pharyngeal insufflation method Wineland and Waters⁵⁹ found a concentration of oxygen in excess of 50% at the glottis.

Masks for the administration of oxygen have no practical significance for general clinical use. They are of value mainly in mining, diving, mountain climbing, aviation and warfare. Various modifications of the original Haldane type of mask have been devised and recently a box mask has been described by Campbell.^{18c}

It has been demonstrated in recent years that oxygen can be administered *subcutaneously* and that it is rather freely absorbed from this channel.^{20,32,49} It is doubtful, however, whether this method is of practical significance.

Percutaneous administration of oxygen is based on the observation that when the skin is surrounded by an oxygen concentration of 37 % or over, it absorbs oxygen more rapidly than when it is surrounded by air.⁵³ In patients with advanced peripheral vascular disease, Starr⁵⁴ observed no change in color of skin or sensation from 50 % oxygen or lower. Concentrations above 80 % caused relief from pain and slowly developing change of color. The change was most marked when the feet were originally very blue. In all cases, the original color of skin slowly returned when the oxygen in the jar was replaced by room air. Starr believes that local oxygen therapy combined with desiccation with heat is a useful supplement to other well-recognized measures.

Oxygen Therapy in Specific Conditions. In recent years oxygen therapy has been used widely and rather indiscriminately. As has been indicated in the preceding discussion, it is of practical benefit in only certain types of anoxemic anoxia, particularly in those associated with diseases of the lungs and of the heart, and with asphyxial conditions.^{31,40} In the following review a few recent contributions have been selected to demonstrate the present status of oxygen therapy in pneumonia and in heart disease.

Pneumonia. It is agreed that oxygen is indicated in pneumonia only when there is cyanosis. Barach^{3c} summarizes the benefit of oxygen therapy in such cases as follows: 1, The bluish color of the lips and nail-bed changes to a pinkish color; 2, the heart rate frequently is slowed; 3, the respiratory rate at times is diminished; 4, the patient is more comfortable and delirium and restlessness are decreased. It is questionable whether statistics indicate a reduced mortality rate in the group of patients treated with oxygen.^{3a,b,13a} The fact, however, that pneumonia patients placed in an atmosphere high in oxygen show the type of improvement described above and that their removal from the oxygen atmosphere may result in accentuation of unfavorable symptoms, including collapse and pulmonary edema,^{3c} clearly indicates that oxygen is a valuable adjuvant in the treatment of pneumonia.

There is no basis for the belief that patients who have been kept in an atmosphere containing a high concentration of oxygen subsequently cannot tolerate lower concentrations.^{3b} Circulatory collapse and pulmonary edema follow the withdrawal of a high concentration of oxygen only when the morbid process is so advanced that the anoxemia is severe under normal atmospheric conditions. If the pneumonic process has improved, the patient can safely be removed from the oxygen tent or chamber. While gradual withdrawal of the high oxygen concentration is advisable in cases of chronic pulmonary or cardiac disease, there is no indication that such patients cannot tolerate air as before. Hence present knowledge would indicate that "oxygen addiction" or acquired tolerance does not occur.

Bronchopneumonia, and postoperative collapse with pneumonia are particularly apt to be associated with arterial anoxemia; hence oxygen therapy is especially indicated.^{14,40} In these conditions secretion and transudate are present in the bronchioles and the atria with maintained capillary circulation. Lobar pneumonia, on the other hand, is not, in the majority of instances, associated with frank cyanosis because in the consolidated area the pulmonary circulation is minimal. In the early stage of lobar pneumonia cyanosis is common because of congestion

and superficial, rapid respiration due to pleural inhibition.^{14,40} It frequently disappears, however, as the condition becomes more advanced. Indication for oxygen therapy may therefore be present in the early, but not in the subsequent stage. In other instances cyanosis may persist.

Cardiovascular Disease. Heart failure is frequently associated with oxygen want resulting from either the stagnant or the arterial type of anoxemia. There is no evidence at present that the oxygen debt in compensated heart disease or the cyanosis associated with slow circulation and with increased peripheral utilization of oxygen (stagnant type of anoxia) is appreciably benefited by oxygen therapy. The arterial anoxemic type of anoxia, on the other hand, should respond to the administration of oxygen. Cyanosis of pulmonary origin occurs quite frequently in cardiovascular disease, as pulmonary congestion with excessive fluid in the alveolar walls and spaces, and alteration in the ventilation with increased pulmonary dead spaces, are the earliest and the most common manifestations of heart failure.^{56,57} The changes in the lungs in heart disease, however, are not entirely of functional nature. As a result of pulmonary engorgement, structural alteration with permanent thickening of the alveolar wall may ultimately develop.⁴¹ The diffusion of oxygen through such an alveolar wall becomes difficult at a time when the carbon dioxide, because of its high diffusion coefficient, can still be eliminated effectively.⁴¹ The anoxia of the myocardium resulting from these functional and structural changes in the lungs can, in turn, exert a damaging effect on the heart, thus leading to a vicious circle. It has been demonstrated on preparations of mammalian heart that reduction of the oxygen supply results in rapid dilatation and failure of the myocardium.¹⁸⁶ In spite of the fact that severe physical exercise does not lower the cardiac glycogen content, breathing an atmosphere containing 6 to 7% of oxygen rapidly leads to a disappearance of as much as $\frac{2}{3}$ of the glycogen content of the myocardium.³⁸ Persistent arterial anoxemia, therefore, exerts a damaging effect on the myocardium.

The beneficial effect of oxygen on dyspnea was first demonstrated by Campbell and Poulton.¹⁹ Levy and Barach,³⁵ Rizer⁴⁸ and Burgess and Chafee¹⁷ have claimed a beneficial effect in coronary thrombosis. Barach and Richards⁴ observed improvement in cardiac failure after 2 to 3 weeks of oxygen treatment, as attested by: 1, increased arterial oxygen saturation; 2, increased arterial carbon dioxide levels; 3, in some cases, a delayed rise in urinary output and disappearance of edema. Katz, Hamburger and their associates²⁸ noted improvement, without diuresis, in some of the cases with heart disease treated in oxygen chambers. They attributed the following changes, both in normal subjects and in cardiac patients, to residence in an oxygen chamber: 1, slowing of the heart rate; 2, decrease in pulmonary ventilation; 3, slight diminution of the vital capacity; 4, increase in arterial oxygen saturation; 5, increase in blood carbon dioxide. Richards and Barach⁴⁷ kept two normal subjects in 45% oxygen for a week. A fall in the pulse rate and a slight rise in blood carbon dioxide levels resulted. No appreciable change was observed in respiratory metabolism, in cardiac output or in excretion of electrolytes or of water. In cases with beneficial response in a group of 28 cases with cardiac insufficiency kept in

atmospheres of 40 to 50% oxygen for from 5 days to 7 months the following changes developed: 1, improvement in dyspnea and in restlessness; 2, restoration of the normal arterial saturation and increase in the blood carbon dioxide; 3, improvement or disappearance of edema. The clinical indications for oxygen therapy, as found by these observers, in the order of their importance are, *a*, dyspnea; *b*, restlessness; *c*, cardiac pain of anginal type; *d*, arterial oxygen unsaturation; *e*, cyanosis; *f*, cough. (The Reviewer feels, however, that these symptoms are indications for oxygen therapy only when they are produced or accentuated by pulmonary changes.) Barach, Richards and Parsons⁵ recently claimed that oxygen therapy may be beneficial in cardiac patients without arterial anoxemia. Increased atmospheric oxygen may exert a beneficial effect on cardiacs, producing the following changes: 1, The oxygen saturation becomes normal or higher than normal and the physically absorbed oxygen is increased. This results in a greater delivery of oxygen by unit of blood flow; 2, there will be better contraction of the myocardium, and consequently improved circulation; 3, the pulmonary ventilation proceeds more efficiently and with less effort. It is obvious from these studies that acute cardiac emergencies, particularly when they are associated with pulmonary edema and arterial anoxemia as in cardiac asthma⁶⁷ and coronary thrombosis, will be benefited by oxygen therapy. If, on the other hand, the collapse and cyanosis in these conditions originate from alteration of the peripheral circulation, little or no benefit can be expected from oxygen therapy.

Asphyxial Conditions. It is evident from the discussion presented that asphyxial conditions resulting from lack of oxygen, either in the atmosphere surrounding the body or within the lung spaces as a result of diseases of the air passages, are ideally suited for oxygen therapy. The literature on this phase will not be cited. In the future development of aviation, and in warfare technique in particular, oxygen treatment will play an increasing rôle.

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RADIOLOGY

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GASTRO-INTESTINAL TRACT.

ONE of the least encouraging chapters in therapy is the one dealing with carcinoma of the gastro-intestinal tract, especially carcinoma of the esophagus and stomach. An editorial⁵ quotes McGibbon as stressing the necessity of early diagnosis, yet there is of necessity a latent period between the earliest carcinomatous formation and the patient's awareness of something amiss, and the duration of this period cannot be estimated. Then the patient may fail to obtain expert advice when

the symptoms manifest themselves or not infrequently the medical attendant treats him for nervous spasm or dyspepsia for 2 to 3 months before the nature and gravity of the complaint are realized. Jackson's records showed an inferential diagnosis of a neurotic condition previously made in 87 of 110 cases of esophagoscopically proved disease of the esophagus, and an analysis of large groups of cases reported showed the average period between the onset of symptoms and the diagnosis to be almost 6 months. Often the patient was sent to the roentgenologist with a vague complaint (difficulty in swallowing), and after the most meticulous examination no evidence of obstruction was found, or abnormal constriction or esophageal spasm. Too frequently the roentgenologist failed to carry out the detailed study of the esophagus long ago practised by Hickey, Barclay, Manges (and others) to bring out slight variations or deviations from the normal. The virulence of the disease itself was an added factor in the poor results obtained in treatment. McGibbon stated that the symptoms and signs of spread by direct extension naturally depended on the level of the growth. The esophagus in its upper two-thirds is in close relation to many important structures, and the spread from growths situated in this locality is more apt to give rise to signs and symptoms than from those situated below the tracheal bifurcation. McGibbon found the most common manifest complication of spread was caused by involvement of the recurrent laryngeal nerves. His findings were in accord with the observations of numerous writers. Certain hopeful surgical measures have been instituted comparatively recently in the treatment of this seemingly hopeless disease. In all cases of doubt, esophagoscopic examination is indicated. Chevalier Jackson stated that if patients suffering from carcinoma of the esophagus have an abundance of water and a full allowance of a well-balanced diet, they will survive for at least 2 years. This rather long survival period should make roentgenologists a little guarded in their statements as to their results with radiation therapy in prolonging life in these cases. More careful Roentgen examination, following a careful technique, reexamining the patient within a day or two if the first examination is negative, preferably at the time of more acute suffering from the difficulty in swallowing, will make for an earlier diagnosis in this condition.

Beilin³ thinks it lamentable that approximately 50% of cancers of the stomach have reached a stage in which not even an exploratory operation is indicated by the time they are seen by the clinician. In the other 50%, in which an exploration is warranted, the growth can be removed in only about $\frac{1}{2}$ of such cases. Thus it will be seen that only 25% of the cases of cancer of the stomach are operated on at a time when an attempt at a cure can be made. This appalling situation is due to many reasons: procrastination on the part of the patient who has "indigestion;" failure to make an early diagnosis; the generally accepted criteria for the diagnosis of gastric cancer are still the late manifestations of the disease; the early syndrome of gastric cancer will have to be popularized and the public made "stomach conscious;" lack of knowledge of the etiologic factors in gastric carcinoma; the absence of any specific serologic tests for its presence; the prevailing attitude of many physicians and of laymen toward the disease, namely, when a diagnosis of cancer of the stomach is made, the condition is

considered incurable and nothing is done. Among the 1000 consecutive examinations of the stomach in this study there were 71 (7.1 %) cancers. The youngest patient was 26 years of age. Levene and Wheatley reported a case of extensive carcinoma of the stomach in a girl, aged 19, who for 5 months prior to admission to hospital had been under the care of her physician for the treatment of a nervous breakdown. This study revealed that the highest incidence of cancer of the stomach occurred in the fifth and sixth decades of life, with the average age being 58 years, and the disease is almost twice as common in males as in females. A review of the literature reveals the difficulty in distinguishing between the benign and malignant lesions at the prepyloric region, the most frequent site of cancer; about 80 % of the carcinomas start there. It is fair to state that any chronic indurating ulcerating lesion occurring at the pyloric antrum within 1 inch of the pylorus and without involving the pylorus should be considered malignant until proved to be otherwise, and that proof of the absence of malignancy in such lesions is obtained only by serial section and careful microscopic examination. Aside from the regional lymph nodes, most metastases lodge in the liver and on the peritoneal surface. After these, the distant nodes, the pancreas, and the lungs are involved in order of frequency. Less than 10 % of the cases metastasize to the lungs. Metastases to bone with cancer of the stomach are more frequent than is usually supposed, these metastases were all of the osteoclastic type and probably were hematogenous. This relative restriction of metastasis is of importance from a clinical standpoint. If metastases are not found in adjacent lymph nodes and in the liver at the time of operation, the chance of more distant involvement having already occurred is relatively slight.

Unfortunately, cancer of the stomach presents no typical early syndrome. When patients present the classical picture of gastric malignancy, as has been so often described, with marked loss of weight, emaciation, pain, vomiting, palpable tumor mass, etc., the disease is advanced. An analysis of his own and the series of others revealed that the early symptomatology of gastric cancer varies in different individuals. However, if one indelibly bears in mind that if there are symptoms in an individual over 40, who complains of indigestion, as well as loss of appetite, nausea, vomiting, abdominal pain, fatigue, loss of weight without obvious cause, unexplained anemia, or any group of the above, one should regard this individual as having carcinoma of the stomach until proved otherwise. It should be popularized to the general profession and laity that the early clinical signs of cancer of the stomach are often so vague and apparently so insignificant, and that usually the earliest symptom is so-called "indigestion;" and in order to make a diagnosis of a beginning cancer, thorough and competent clinical and roentgenologic examinations must be made at the time that the individual first presents himself, for the discovery of a carcinoma at that time will remarkably increase the percentage of cures.

Avery¹ found little available information in the literature on the subject of syphilis of the esophagus. One author stated that less than 100 cases, many not proven or authentic, had been reported. Lawrence stated that the condition was diagnosed as such in only 1 or 2 of every

thousand cases in which lesions were present. Lukens and Ono found only 12 cases of tracheo-esophageal fistula attributable to syphilis in their review. Another author found 4 syphilitic lesions of the esophagus in 350 consecutive cases of dysphagia. Still another stated that thousands of esophageal examinations might fail to reveal a single case of syphilitic involvement. The congenital form does occur, but it is rare. There is an esophagitis in the secondary stage often associated with mucous plaques and ulceration. Gumma and contractural sclerosis are seen in the tertiary stage. Esophagitis occurs more often in the middle half, while gumma usually involve the upper or lower thirds. There may be induration and spasm; a gumma may ulcerate and rupture; sclerosis and contracture may become pronounced, with almost complete stenosis. Dilatation above the lesion is usually not a striking characteristic. Primarily extraesophageal lesions have been reported, with secondary involvement of the esophagus. A history of transitory attacks of mild dysphagia, gradual in onset, often of from 4 to 12 months' duration, with difficulty only in swallowing solids at first, then semisolids, and later liquids, is the most suggestive symptom. Loss of weight, anemia, and asthenia occur in the late stages. Sclerosis and contracture may become pronounced, with almost complete stenosis. Patients rarely have pain though there may be some with laryngeal involvement. Diagnosis, while still difficult, has been facilitated in recent years by Roentgen study, esophagoscopy, and serologic investigation. The prognosis is good except in advanced stenosis. The treatment in the early stages is that for syphilis; successful treatment in the late stages can only be carried out by the esophagoscopist, because of the necessity of dilatation of contractural sclerosis and stenosis. The author reports 2 cases successfully treated.

Baum² reported a case of esophageal-gastric carcinoma in a male, aged 53, in which microscopic examination of tissue in 1929 revealed a squamous-cell carcinoma with hornification. Roentgen examination revealed a marked dilatation of the lower end of the esophagus, with a tumor mass distal to this involving the esophagus and cardiac portion of the stomach. There were no pulmonary metastases. High voltage Roentgen ray therapy, the protracted fractional method, was immediately instituted. Forty-two treatments were given over a period of 69 days, the average dose per treatment being 480 r units. After a month of treatment the patient was able to take solid food and radiographic examination after completion of treatment showed only a slight degree of irregularity at the cardiac end of the esophagus, corresponding to the site of the original lesion. Seen and examined 7 years later, the patient had carried on his usual occupation for 4 years and was able to eat a general diet without pain. The fluoroscopic and radiographic examination showed no evidence of obstruction in any portion of the esophagus.

English⁷ reported a case of ectopic stomach in which Roentgen examination showed the esophagus extending far below the diaphragm and at least $\frac{2}{3}$ of the stomach, together with the duodenum contained in the sac of a large inguinal hernia. A loop of small intestine and a portion of the transverse colon were also found within the sac. Reëxamination with the patient in the recumbent position and the hernia reduced, showed no intrinsic lesion in the gastro-intestinal tract. At operation, the hernia was found to be of the simple indirect type.

Elward⁶ reported a case of herniation of the stomach through the esophageal hiatus and a diverticulum of the middle third of the esophagus in the same patient. The existence of the hernia was confirmed by surgical investigation and successfully closed.

There is no single procedure which throws more sudden light on a vague or obscure clinical picture than the finding of a hernia through the diaphragm. In the vast majority of cases the condition is not even suspected from the clinical point of view. Symptoms which are present vary widely; at times they may be chiefly respiratory, cardiac or gastro-intestinal, but at other times eventration or actual hernia is discovered in a person who has no complaint whatever. Newcomet and Spackman¹² discuss the methods of defining the hernia, which include roentgenographic and roentgenoscopic examination, with the introduction of gas into the stomach, gentle manipulation in several positions, watching the effect of the diaphragmatic motility on forced respiration and viewing the relation of the diaphragm and abdominal viscera in various postures. It is always advisable to do the general fluoroscopy first in various postures before partially filling the stomach with gas, and to use the opaque meal last. It must be borne in mind that there are hernias which do not contain the stomach and in these the difficulty of recognition is somewhat increased. Careful routine examination of all thoracic and gastro-intestinal cases has elicited but 1 case of diaphragmatic hernia in every 4324. Eventration in their experience has been symptomless and does not inconvenience the individual. Diaphragmatic hernia, however, is a serious matter and the symptoms are apt to be progressive.

As a direct means of establishing a diagnosis of appendicitis the Roentgen ray offers little aid; it is often misleading and not infrequently leads to an erroneous decision. Its greatest usefulness, however, is in the differential diagnosis, eliminating the more common gastro-intestinal and urinary tract conditions which clearly mimic appendiceal disease. Feldman⁸ considers it far better to make innumerable unnecessary investigations than to have a patient subjected to a useless and often harmful operation. Many patients, especially those of a neurotic tendency, find themselves in a worse state and are much more difficult to control than if they had not been operated on. A review of the literature on this subject confirmed this opinion. A study of several groups, including his own, showed that in the majority of instances patients who were unrelieved of their symptoms after operation for chronic appendicitis had little or no pre-operative Roentgen ray study. Roentgen examinations after operation in his own series revealed peptic ulcer (gastric and duodenal) in 36.5%, gall bladder lesions in 26% and genitourinary pathologic lesions in 6%. His findings approximated those of similar studies by other observers. Feldman feels that in no instance should operative procedures be undertaken for chronic appendicitis until all other conditions have been thoroughly eliminated. The Roentgen method of investigation is of the greatest importance as an aid in the ultimate diagnosis.

Lesions of an inflammatory character or those associated with some process which has an inflammatory reaction as a background, affect the motor characteristics of the small intestine through three different channels, namely, innervation, blood supply and mechanics. Innerva-

tion is a term used in the broad sense and must not be considered as indicating a specific nerve reaction alone or a neurologic lesion. In all cases of this group there is a disruption of normal peristaltic action or muscular tone or both. Since activity and tone of smooth muscle depends on nerve stimuli, the lack of muscular activity evidenced in all cases of this group may be associated with changes in innervation. This may be either general or local. These changes in innervation may have their origin in the central nervous system but more likely in the sympathetic nervous system. They are probably due to a toxic effect or direct pressure on Auerbach and Meissner plexuses. An allergic phenomenon might be a better term if one could explain allergy. Under this heading Cole and Pound⁴ grouped ileus, migraine, enteritis and pancreatitis. Ileus is an atonic dilatation of the small intestinal coils with marked distention from gas and is generally considered paralytic. It may be associated with an inflammatory process in the peritoneal cavity or may be a reflex manifestation from some more remote cause. The radiologic diagnosis of ileus depends upon the appearance of the gas-filled coils seen in plain films of the abdomen. The differentiation from a mechanical obstruction is very difficult and at times impossible. Roentgenographically enteritis is characterized by no evidence of obstruction or gas in the small intestine in the plain film. Barium studies show a very definite interference with the motor phenomena evidenced by a marked diminution of activity, a slight atony, or dilatation of the filled coils and a delay proximal to the area of greatest involvement. The amount of intestinal gas is not markedly increased and the barium has a tendency to stagnate in segments.

Migraine exhibited an abnormal dilatation of the small intestine, with a conspicuous absence of the major and minor motor phenomena leaving only the plica circularis as an anatomic finding. In acute pancreatitis changes in the mucosal pattern, especially noticeable in the border of the duodenum adjacent to the pancreas were noted, with variations in the diameter of the lumen. Lack of gas in plain films with a fluid content of the lumen was very suggestive to them of mesenteric thrombosis. When the loops were filled with a barium meal they showed an atonic dilatation with no visible peristalsis.

Mechanical obstruction secondary to adhesions was characterized by the festooning of dilated gas-filled small intestinal coils across the abdomen in stepladder formation.

Intrinsic inflammatory lesions exhibited alteration in the structure of the wall and lumen. The distal portion of the ileum seemed to be the site of preference in those lesions. There were two main types of involvement, the isolated or continuous lesion and the so-called skip lesion. In the continuous type of lesion the lumen was narrowed and the walls were irregularly thickened. The barium passed through the altered lumen in an irregular, narrow stream. The lumen margins were serrated in appearance. The speed with which the barium passed through the involved area depended on the amount of local or current irritability. The adjacent normal coils appeared to be displaced from the involved area, due to the thickening of the walls of the diseased portion. The skip lesion usually involved shorter segments, and the irregularities of the lumen again depended on the stage of progress of the inflammatory reaction. Between the areas of local contracture there

were areas of compensatory dilatation or relatively normal appearing lumen. Some of these lesions entirely encircled the lumen, others were limited to one side, shown by the absence of normal markings on the mesenteric border and exaggerated markings on the antimesenteric border.

Conditions associated with partial deprivation of certain vitamins, of protein, and of important organic elements ("deficiency states") embrace those reactions occurring in sprue and the lesion generally referred to as "ulcerative colitis" exhibited delayed forward progress instead of increased speed in the small intestine. Changes in the appearance of the mucosal markings were found from the duodenum to the cecum. The normal markings were wider—that is, thickened—and frequently bizarre in appearance. The motor phenomena were disrupted.

That the pre-operative diagnosis of the condition variously known as "terminal ileitis," "regional ileitis" and "chronic cicatrizing enteritis" is almost entirely dependent on correct Roentgen examination and interpretation was the opinion of Sproull.¹³ This condition is marked by a characteristic subacute or chronic necrotizing and cicatrizing inflammation and is clinically featured by symptoms resembling those of ulcerative colitis, namely, fever, diarrhea and emaciation, leading eventually to an obstruction of the small intestine and to the occurrence of a mass in the right iliac fossa requiring resection of the involved intestine. Originally, it was stated that the terminal ileum only was involved and that the disease never attacked the large intestine; later experience has shown that the disease may involve any part of the small intestine except the duodenum, and cases have been reported of simultaneous involvement of the terminal ileum and cecum. The Roentgen findings in regional ileitis vary with the stage of the disease at which the examination is made. In the acute stage of the disease the diagnosis of appendicitis is usually made and at this period Roentgen examinations are uncommon. In the subacute stage, the Roentgen findings in the affected segment or segments are moderate narrowing of the lumen of the bowel, irregularity of the margins of the bowel, some degree of local stasis, rigidity of the bowel wall, and a mucosal relief pattern of the finger-print-depression type resembling that produced by polyposis. The roentgenologic appearance of the later stage (commonly called the fibrostenotic stage) in the terminal ileum, where this stage is most commonly seen, consist of: 1, a filling defect of varying length in the terminal ileum; 2, dilatation of the loops of ileum proximal to the lesion and the presence of puddling and fluid levels in this area; 3, abnormality in contour of the last filled loop of ileum; 4, the presence of a string-like shadow of barium, of varying length, which represents the area involved and which Kantor calls the string sign. The string sign does not always show the extent of the area involved. In some cases the fibrostenotic changes are limited to a comparatively small area of the diseased intestine. In such circumstances the string sign will show the extent of the fibrostenotic area while the remainder of the involved intestine will present the Roentgen findings characteristic of the subacute stage. Where the colon is involved, the barium enema is valuable and may reveal characteristic filling defects, abnormal mucosal relief pattern, or fistulous tracts between the small and large intestine. The three

most important diseases to be differentiated are appendicitis, ileocecal tuberculosis and ulcerative colitis.

In discussing diarrhea as a symptom, Golden⁹ stated that the failure to demonstrate disease of the colon does not necessarily mean that no organic basis exists for the symptom. Disturbances of the small intestine also may cause diarrhea and deserve study by Roentgen methods when the large intestine is found to be normal. Diarrhea was either a presenting or an important symptom in 9 of 11 cases of non-specific granuloma of the small intestine (regional ileitis). Diarrhea, either continuous or alternating with constipation, was present in different series of tuberculosis of the intestine in percentages varying from 66 to 27. Tuberculosis is usually associated with phthisis but may occur in the absence of pulmonary disease. Both ileum and cecum are usually involved; in rare cases, a large localized tuberculous ulcer may be found in the large intestine. Diarrhea is the presenting symptom of chronic steatorrhea, non-tropical sprue, celiac disease in infants, adult celiac disease and tropical sprue; all apparently based upon the same physiologic disturbance—lack of an essential substance or substances—and considered essentially the same disease. Diarrhea sometimes occurs without either clinical or Roentgen evidence of organic disease. The symptom is usually attributed to psychic or nervous influences; it is infrequently associated with lymphosarcoma of the small intestine and did not occur in any of the 11 cases of benign neoplasms of the small intestine found at necropsy in his series. It occurred in only 4 of 20 cases of proved malignant disease of the small intestine; with intussusception of the small intestine it rarely, if ever, occurs.

The most common roentgenologic finding in cases of small bowel tumor, whether they are benign or malignant, is intestinal obstruction. In such cases the Roentgen examination is of great value in determining the presence of obstruction and its location, but the actual causes of the obstruction is usually obscure. There is one type of malignant small bowel tumor which is extraluminal and non-obstructive. Arising in the wall of the small bowel, these tumors grow away from the lumen and out into the mesentery, forming large external masses. The lumen of the involved segment, instead of being stenosed and obstructed, is usually irregular dilated due to necrosis and ulceration within the tumor mass. In such cases the Roentgen findings are very characteristic. Lingley¹⁰ reported 5 such cases with the Roentgen findings. The involved segment of the small bowel was irregular in outline with obliteration of the mucosa and with moderate to marked dilatation throughout the lesion. There was no obstruction but the involved area could be made visible even after the barium column had passed beyond because of a coating of barium adhering to its ulcerated surface. In most cases a large mass could be palpated corresponding to the defect in the bowel, this mass often being very large in comparison with the small area of intestine involved.

Martin¹¹ presented 19 cases of proved "lymphoblastoma" involving the gastro-intestinal tract, studied at the Massachusetts General Hospital since 1925. This group included Hodgkin's disease, lymphosarcoma, lymphoma, leukemia and aleukemia. The distribution of the lesions in the stomach alone, in the stomach and intestine, and in the intestine alone was tabulated with the other cases reported in the litera-

ture. Lymphoblastoma has been found as a primary lesion in all parts, of the gastro-intestinal tract except the esophagus. In this organ, it may appear as a direct extension from a lesion in the stomach or from the epiglottic folds. The majority of the lesions are found around the pylorus and ileocecal region. When found around the pylorus, there is a marked tendency for the disease to spread beyond the pyloric valve and involve the duodenum. The great majority of the lesions start in the submucosa. Of great diagnostic importance to the roentgenologist is the pathologist's description of the mucous membrane of the involved stomach. In 70 % of the cases, the rugæ of the stomach were described as thickened and distorted, and in 35 % were so greatly distorted that the pathologist described them as resembling the cerebral convolutions. The involved cecum shows the same type of thickening and distortion as the gastric mucosa. The anatomic changes that are of value to the roentgenologist in gastro-intestinal lymphoblastoma are thickening and distortion of rugæ; displacement and pressure defects of the fundus; a double lesion of the gastro-intestinal tract; a lesion of the pylorus that extends over the valve end and involves the duodenum; and changes in the duodenal loop associated with pressure defects on the fundus of the stomach and splenic flexure (enlargement of the head of the pancreas associated with an enlarged spleen). When the lesion was located in the ileocecal region, it was not uncommon for it to produce mandarin-sized tumors which at times caused invagination of the ilium into the cecum. It was not rare to find tuberculous and lymphomatous ulcers side by side in the same part of the intestine. The treatment of gastro-intestinal lymphoblastoma usually requires both surgery and deep Roentgen therapy. Surgery offers a definite possibility of cure.

True neoplasms of the colon manifest themselves roentgenologically by signs so consistently distinctive as to be practically pathognomonic. When these characteristic roentgenologic manifestations of neoplasm are not elicitable, the Roentgen diagnosis of non-neoplastic tumor is made simply by exclusion, since no alternative diagnosis is possible. With this preface Weber¹⁴ contrasts the roentgenographic images of the neoplastic and the non-neoplastic tumefactive lesions of the large intestine. The filling defect produced by inflammatory tumefactions is essentially a constriction of the lumen, embracing only a part of one of the divisions of the large intestine, but it is usually a longer defect than the one associated with neoplasm. The filling defects fade off gradually, almost imperceptibly, into the normal contours of the intestine proximal and distal to the constricted area. Destruction of the mucosa may or may not take place, and when it is observed it is practically always in association with those inflammatory tumors caused by an etiologic agent which under other circumstances causes ulcerative colitis. The tuberculous, amebic, and the streptococcal granulomas are the principal examples of this group of inflammatory tumefactions. The most important pathologic changes are found in the submucosal structures, and while the mucosa has always undergone some pathologic change, it may be unbroken throughout the entire extent of the lesion. Rarely, multiple inflammatory lesions are encountered in the same colon. Combined involvement of ileum and cecum is commonly seen when an inflammatory tumor involves this

region, a phenomenon never seen with neoplasm unless perforation has taken place. There are no fundamentally reliable roentgenologic signs by which the various etiologic types of inflammatory tumor can be distinguished from each other.

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PHYSIOLOGY

PROCEEDINGS OF

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SESSION OF MARCH 15, 1937

Vitamin B₁ and Carbohydrate Tolerance. CHARLES F. CHURCH and DOROTHY V. WHIPPLE (Department of Pediatrics, University of Pennsylvania, and Children's Hospital of Philadelphia). Withdrawal of vitamin B₁ from the diet of rats results in immediate and progressive decline in daily growth increment. Voluntary food intake roughly parallels growth increment but lags behind it. This suggests that the inability to form new tissue is a primary defect in vitamin B₁ deficiency. Increasing the ratio of protein and mineral salts to the carbohydrate in the diet did not alter growth increment or food intake. Glucose tolerance tests indicated that diminished tolerance for carbohydrate occurred in the late stages of vitamin B₁ deficiency when the blood sugar mounted to extraordinary heights. Insulin did not reduce this hyperglycemia nor alter the symptoms of the disease. There was little or no disturbance of glucose tolerance in depletion, at a time when growth increment and food intake were rapidly diminishing. These results give indirect evidence in favor of the hypothesis that vitamin B₁ plays an essential rôle in the synthesis of fat.

Vitamin B₁ and the New Synthesis of Fat. DOROTHY V. WHIPPLE, CHARLES F. CHURCH, and HAROLD STEVENS (Department of Pediatrics, University of Pennsylvania, and the Children's Hospital of Philadelphia). Rats on fat-free diets containing adequate vitamin B₁ were able to gain more weight than isocaloric control animals not receiving the vitamin. The average body composition of the animals receiving vita-

min B₁ and their mates of isocaloric intakes but not receiving the vitamin were (in per cent) as follows: with vitamin B₁ water 64.9, fat 9.4, protein 18.5, ash 5.8; without vitamin B₁ water 67.8, fat 3.3, protein 21.2 and ash 5.9. The animals receiving vitamin B₁ gained 13.5 gm. more weight than the animals not receiving the vitamin. Fat accounted for 6.5 gm. and water for 6.2 gm. of this total.

Respiratory quotients, after the subcutaneous injection of 1 gm. of glucose in similar pairs of animals showed quotients below unity for the deficient animals and above unity for the controls. The average of 17 determinations on 8 rats, taken during the progress of vitamin B₁ depletion was 0.85. The average of 17 determinations on 9 isocaloric control rats receiving an adequate amount of the vitamin and made on the same day and under the same conditions as the deficient rats was 1.15. Crystalline vitamin B₁ raised the R. Q. of rats showing severe symptoms of B₁ deficiency. The average of 8 determinations, after the injection of 1 gm. of glucose in 7 rats showing severe symptoms, was 0.79; the average of 7 determinations on these same rats immediately after the injection of 0.1 mg. crystalline vitamin B₁ was 1.48.

A hypothesis is suggested that vitamin B₁ is essential for the synthesis of fat in the animal body.

Poikilothermic Changes in Man and Their Effect on Respiratory Exchange. H. C. BAZETT, S. GOLDSCHMIDT, B. MCGLONE and L. SRIBYATTA (Laboratory of Physiology, University of Pennsylvania). If a subject be immersed in a moderately cool bath (30 to 32° C.) the rectal temperature after an initial rise slowly falls with little sensation of cold. If the bath be then raised 0.5 to 2° there is a marked sensation of peripheral warmth, resulting in vasodilatation, and flooding of the central areas with blood from the cooled skin. The mean body temperature is at this time rising, but the rectal temperature shows a rapid fall. Under such conditions the lowered rectal temperature is usually accompanied by a lowered rather than raised oxygen intake, the CO₂ output is decreased to an even greater extent, and respiration is depressed. There is a marked fall of the respiratory quotient (to below 0.7), a marked reduction in alveolar O₂ tension, and usually a rise in alveolar CO₂ tension. The condition is therefore the opposite of that seen with hyperpyrexia.

The changes are associated with the change in rectal rather than in mean body temperature, and are presumably dependent upon the respiratory adjustments necessitated by the reduced capacity of blood proteins (or proteins in other tissues) to bind base at the lower temperature. The changes resemble the retention of CO₂ that has been described in frogs and alligators on cooling, except that the respiratory response increases the CO₂ tension, while in the cold blooded animals this tension falls.

On Depolarization of the Muscle and Nerve Membranes by Organic Substances. RUDOLF HÖBER (Laboratory of Physiology, University of Pennsylvania). On the basis of the frequently discussed conception, that the wave of discharge following excitation of a muscle or a nerve fiber is accompanied by some chemical or physicochemical reaction which temporarily abolishes the selective cation permeability of the

surface film of the fiber, an attempt has been made to find organic compounds comparable in some way to products of metabolism connected with excitation, which, applied from the outside, would bring about depolarization dependent upon an increase of permeability to ions.

Experiments performed with sartorius muscles and sciatic nerves of the frog showed that organic cations, anions and nonelectrolytes are able to depolarize the membranes with a potency parallel to their ability to cytolys (f. i. caprylate, nonylate, oleate, taurocholate; dialkylamines; alkylcarbamates). In this respect the muscles were found to be more sensitive than the nerves. The effects are fairly reversible unless duration and concentration are unduly high.

These observations afford an explanation of the change of permeability in question as follows: free fatty acids or their ions might be released during excitation from phosphatides which are supposed to be normal constituents of the plasma membranes. Due to their polar configuration, surface activity, and lipoid solubility they would be capable of bringing about some degree of cytolysis, i. e., alteration of the molecular distances in the surface film.

Reflexes from the Carotid Body to the Respiratory Center. J. H. COMROE, JR., and CARL F. SCHMIDT (Laboratory of Pharmacology, University of Pennsylvania). In dogs anesthetized with chloralose and with depressor nerves cut, the respiratory reflexes aroused in the carotids by chemical agents (lobeline, cyanide, increased CO_2 and decreased O_2) were investigated from the standpoints of (a) site of origin, and (b) physiologic significance. Origin was found to be in the carotid body, for intracarotid injection of lobeline or cyanide failed to stimulate breathing when artery supplying the carotid body was clamped; pressure receptors of the carotid sinus are not involved, for lobeline reaching the latter but not the carotid body had no effect while typical hyperpnea resulted when the drug reached the carotid body but not the carotid sinus. Either CO_2 excess or O_2 lack in the fluid used to perfuse one carotid body produced hyperpnea, but the necessary changes in CO_2 were beyond the ordinary physiologic range. To test the physiologic significance, an animal prepared for perfusion of one carotid body was made to breathe O_2 , CO_2 in O_2 , and N_2 or N_2O , in succession; at the height of each effect blood was drawn from an artery, heparinized, and shortly afterward pumped through the carotid body; thus the systemic response could be compared with the reflex one and the changes were within limits known to be physiologic. In 44 such experiments it was found that: (a) reflex hyperpnea occurred in every case when blood O_2 was reduced by 4 vols. % or more; whereas to get an equally constant response from increased CO_2 , blood CO_2 had to be increased by more than 16 vols. %; (b) reflex (carotid body) hyperpnea of anoxemia was greater than, equal to, or somewhat less than that due to inhalation of the gas, depending on whether neither carotid body, or one, or both were receiving blood during the inhalation; but with CO_2 excess, the systemic response was always much greater than the reflex, and the activity or inactivity of the carotid body or bodies during the inhalation made no difference; (c) threshold of the carotid body receptors to CO_2 was never below an increase of 4 vols. %, whereas an increase of

less than 2 vols. % increased breathing about 50 %, and an increase of 2 to 4 vols. % doubled it, when acting on the center; reflex hyperpnea of CO_2 excess was nearly always much less than reflex hyperpnea of anoxemia in the same animal; to get a reflex hyperpnea from CO_2 excess equal to that produced by O_2 lack blood CO_2 had to be increased more than 16 vols. %. These results justify the belief that reflexes from the carotid body, though essential to the hyperpneas of lobeline, cyanide, and anoxemia, have little or nothing to do with the response to CO_2 over the usual physiologic range; receptors of the carotid body seem more influenced by O_2 lack than by CO_2 excess and are very much less sensitive to changes in CO_2 than the cells of the respiratory center.

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ORIGINAL ARTICLES.

THE BLOOD-CHOLESTEROL RESPONSE TO INTRAVENOUS
THERAPY IN PERIPHERAL ARTERIAL DISEASE.

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(From the Medical Service of Dr. A. L. Garbat.)

VARIOUS therapeutic procedures have been advocated for the relief of symptoms due to peripheral vascular lesions. These have included such measures as the intravenous administration of hypertonic solutions, typhoid vaccine therapy and passive vascular exercises (Pavaex therapy). We have been particularly interested in the intravenous forms of therapy, and have been cognizant of the fact that their use in these cases has been based upon purely empirical data.

In 1934, I⁴ reported the value of intravenous physiologic saline therapy in a case of polycythemia vera, with painful ulceration of the foot, due to peripheral arterial disease. Since that time we have employed solutions of sodium iodide as well as the chloride, in various concentrations, in similar cases of painful ulcerative lesions of the extremities due to peripheral arterial disease, with very satisfactory results.

During the period of treatment, our cases were carefully studied in order to determine whether any significant changes could be detected in the blood chemistry that might be of some diagnostic or therapeutic help. Certain striking and characteristic changes did occur in the blood cholesterol and it is these observations which constitute the basis of this communication.

Before entering upon the report of our observations, however, it might be well to review some well-established facts regarding the

chemical changes in peripheral vascular lesions, and the part played by such substances as cholesterol, chlorides, iodides and calcium in this disease process.

Arteriosclerosis and Calcification. As is well known, elastic tissue is particularly prone to early calcification, and it is not uncommon to see the elastic laminæ of the small arteries calcified in an apparently selective manner. The deposition of the calcium can only be explained on theoretical conclusions and such explanations must be accepted until more definite experimental data are obtained. Thus Lichtwitz⁷ advanced the idea that precipitation of the colloids in areas of degeneration decreases the amount of the crystalloids which can be held in solution. As a result of this the least soluble salts, those of calcium, are precipitated. By the laws of osmotic pressure, more calcium will then enter to establish equilibrium, be precipitated, and make way for more calcium until the amount of the deposit prevents further osmotic diffusion. Wells¹² contends that the deposition of calcium salts in areas of tissue degeneration depends upon one or more of several factors, such as tissue reaction, protein content, and so on. In many of the cases of peripheral arterial disease that have come under our observation, the degree of calcification was quite marked and could very easily be demonstrated by roentgenograms.

Chlorides and Iodides in Relation to the Body Fluids. The work of Loeb, Atchley and Palmer⁸ is of extreme interest in this connection. They found that edema fluid contains more chloride and less potassium than the blood serum, while the sodium, carbonic acid, calcium, urea, glucose and non-protein nitrogen exist in approximately the same concentrations in the serum as in the edema fluid. The reason for this variation in the chloride content of serum and edema fluid was found to be due to a difference in the concentration of the proteins of the two fluids. This effect was quite similar to that obtained in a simple membrane equilibrium. Van Slyke, Wu and McLean,¹⁰ in an extensive study of the electrolyte and water distribution in the blood, have demonstrated the validity of the application of this purely physiochemical concept to the problems of equilibria in the blood and tissues. It might also be mentioned here that a similar phenomenon is noted in diabetic acidosis, where dehydration with considerable loss in blood chloride has been shown to occur and where the symptoms of dehydration clear up only after the administration of a definite amount of chlorides to the blood.

The rôle of iodine in the dissolution of necrotic and fibrotic material has also received considerable attention and has had ample clinical substantiation. Jobling and Peterson⁵ were the first to offer a theoretical explanation for such action, particularly with respect to gumma formation. These investigators maintained that the softening and removal of necrotic fibrotic material depended normally upon the action of a tryptic ferment. In the case of the

gumma, for example, the lesion persists and remains firm because it contains large quantities of so-called antitryptic substances which are of lipid nature, being combinations of unsaturated fatty acids. Whether these lipid substances contained cholesterol was not determined at that time. Their power of antagonizing the normal tryptic ferment was found to depend upon their unsaturation, which in turn could be completely satisfied by iodine.

Cholesterol. Considerable detailed work has been published regarding the chemical and physiologic properties of this substance. Recent studies in the vitamin field, for example, suggests that cholesterol may have more active functions than had hitherto been appreciated.³ It is our purpose, however, only to mention those facts which have a direct bearing on our present problem.

Cholesterol is an alcohol which may exist both free and in combination with fatty acids. It is the least soluble constituent of the red blood corpuscles' stroma and accumulates in extravasations as large thin plates. In various degenerative processes in the body, cholesterol is characteristically found in increased amounts. In endarteritis obliterans, various investigators¹ have reported finding an increased amount of cholesterol in the arterial walls. It has also been repeatedly observed that certain poisons like saponin failed to effect hemolysis in immunized animals, due to the increased amount of cholesterol present. The defensive mechanism of the animal to such toxins seems to be an increased mobilization of this substance in the blood, where it appears to bind and neutralize the poisons in much the same manner as the antitoxins neutralize toxins.¹¹ On the other hand, phagocytosis has been found to be definitely inhibited by cholesterol.² It is of further interest to note that in studying the sedimentation rate of the red blood corpuscles, Kurten⁶ found that increased amounts of cholesterol are found to be present where the sedimentation rate is increased and that the addition of cholesterol to a specimen results in an increase in its sedimentation rate.

Procedure. The patients included in the present studies, all presented, at the time of admission, signs of peripheral arterial disease of the occluding type, associated with painful ulcerations of the extremities. The patients are kept at bed rest for the entire period of treatment, lasting from 4 to 6 weeks. Complete chemical blood and cholesterol determinations are made on admission. The cholesterol determinations are repeated about every 4 to 6 days. Intravenous therapy, consisting of 200 cc. of a 2% solution of sodium iodide in physiological salt solution is given every other day. Where idiosyncrasies or unusual systemic reactions are observed, indicative of iodine intolerance, a 2% sodium chloride solution is substituted. These solutions must be freshly prepared and do not require buffering. Solutions that are more than 24 hours old should be discarded as they have been found to produce severe and unpleasant systemic reactions. The local lesions are treated with dry heat and are properly protected from pressure and other possible traumatic injury. Where a diabetes coexists, adequate dietary treatment with insulin, if necessary, is given.

Observations. The present report is based on 12 cases. Their ages vary from 41 to 73 years; 8 are males and 4 females. In 1 case the lesion was secondary to an embolus that had occurred postoperatively 10 years prior to the onset of the ulceration of the extremity; 3 had a complicating diabetes; 4 required more than one course of treatments. The entire group showed the same response as manifested by a cessation of the pain after receiving several of the intravenous treatments and complete healing of the ulcerative lesion at the end of the period of treatment. The shortest period during which the patient remained free from pain or recurrence of the ulceration after a single course of treatments is 2 months, while the longest period is 18 months, with an average period of 8 months for the entire group. The longest period of follow-up for the entire group, with freedom from pain or ulceration, is 5 years. The only significant changes noted in our blood chemical studies during the course of treatment relates to the blood cholesterol (Table 1) and these changes were shown by each case in the group.

Blood-cholesterol Response. The initial blood-cholesterol level of our patients with peripheral arterial disease, accompanied by pain and ulceration shows either a subnormal or low normal value. The lowest blood cholesterol in our series is 80 mg. per 100 cc. of blood serum. After several treatments with the chloride or iodide solutions, a sharp rise in the blood cholesterol is invariably noted, which is followed by a subsequent fall to the normal level as the treatment is continued. Table 1 shows the type of blood-cholesterol curve obtained during the course of treatment in these cases. In some of the cases in Table 1, the height of the cholesterol response amounted to almost 3 times that of the initial figure.

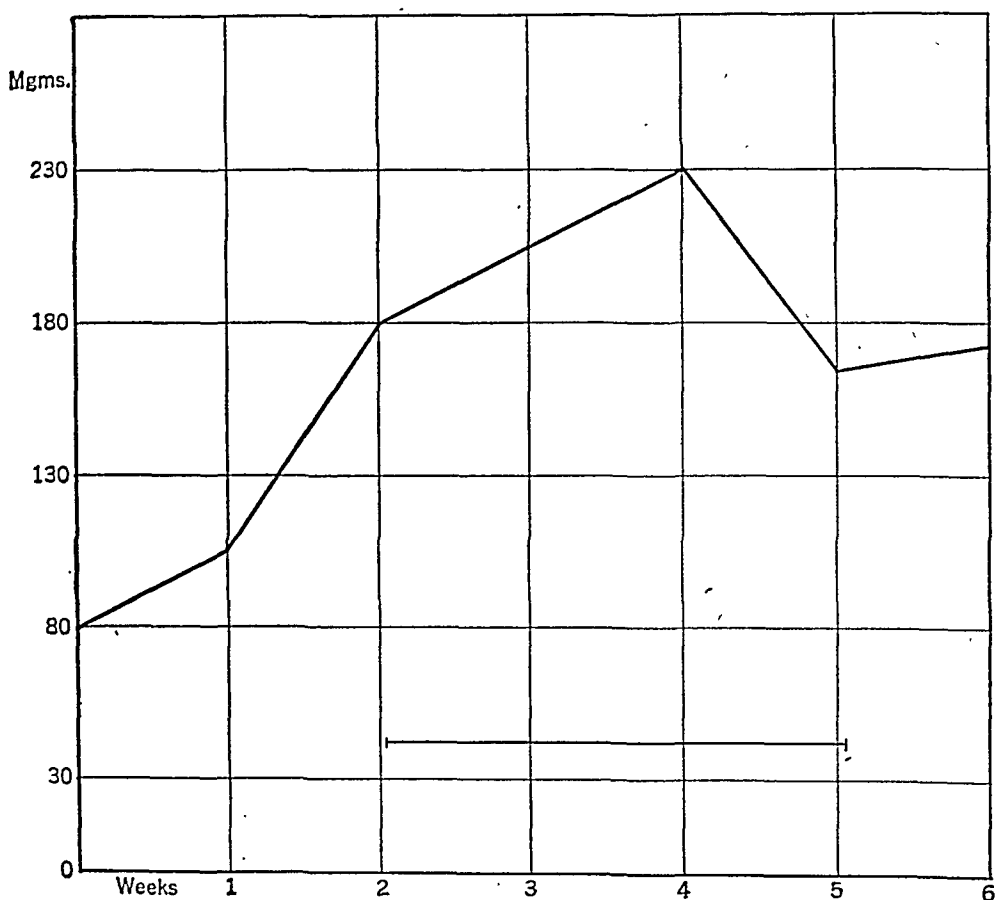
TABLE 1.—BLOOD CHOLESTEROL IN PERIPHERAL ARTERIAL DISEASE.

Case.	Age.	Sex.	Cholesterol determinations.						Blood cholesterol with recurrence.
			1st.	2d.	3d.	4th.	5th.	6th.	
R. A.	73	F	110	150	210	285	240	220	130 mg./100 cc.
A. S.	56	M	80	105	180	210	230	160	
J. E.	54	M	125	150	190	230	250	200	150 mg./100 cc.
S. K.	41	F	130	170	200	225	240	180	
E. T.	59	M	170	210	285	260	210	200	
M. T.	70	M	165	190	245	230	210	210	
L. W.	65	F	100	140	165	240	205	180	135 mg./100 cc.
O. S.	70	M	160	180	296	276	215	166	
F. K.	63	M	198	230	245	285	240	205	
H. H.	58	M	175	200	230	265	220	185	
T. F.	54	F	150	185	260	240	220	200	
B. G.	64	M	135	170	230	220	200	210	

Several significant observations, however, may be pointed out: (1) The fact that the initial blood cholesterol is either subnormal or normal. (2) The lower the initial blood cholesterol, the more rapid and more marked is the relief from pain and the healing process. (3) With the recurrence of the symptoms, the blood cholesterol is again found to be lowered, considerably below the level at the termination of the previous course of treatments. We

have noted that this decrease in the blood cholesterol occurs some time before the recurrence of the pain and ulceration. By making use of this finding, the patient may be spared a great deal of unnecessary pain and discomfort, by its employment as an indication for the institution of further treatment.

Discussion. In the small series of cases that we now have available, it is, of course, very difficult definitely to evaluate the findings. While no attempt can be made at present to interpret the



GRAPH 1.—Curve showing typical blood cholesterol response to intravenous treatment with chloride and iodide solutions.

results in terms of pathologic processes, it is interesting to attempt to fit in these observations with the available data and theoretical explanations that have been published regarding peripheral arterial disease.

As is well known, arteriosclerotic lesions, varying from slight thickening to a severe form of obliterating endarteritis, contain pathologic deposits of glycerine and cholesterol esters. These substances readily split up and become saponified, with the liberation of the soluble glycerine and crystalline cholesterol. Of the soaps formed with the resultant fatty acids, calcium soaps are

insoluble and remain where they are formed, until the advent of phosphates in the circulating blood causes another reaction to occur whereby the calcium becomes deposited in the form of hard calcium phosphates. The phosphoric acid in this reaction is supplied principally by the nucleoproteins and lecithins which usually undergo decomposition whenever tissue degeneration takes place. The source of the fatty acids is likewise not difficult to explain, as they are abundant in fatty degeneration processes which usually go on in areas of degeneration.

The deposition of the calcium salts in the wall of the arterial vessels thus continues, as the damage to the vessel wall increases. Cholesterol plays a very important rôle in this process. With the first signs of damage in the walls of the blood vessels, fatty degeneration with the resultant liberation of fatty acids soon takes place as part of the degenerative process. There is present in such lesions antitryptic substances⁵ which have been described as having chemically the properties of unsaturated fatty acids. The first reaction to the above-described degenerative process is a demand upon the available supply of cholesterol as Nature's means of counteracting the fatty acid liberation, with the resultant formation of cholesterol esters. As the process becomes more generalized, a greater demand is made upon the available body cholesterol. This explanation is actually borne out by our findings of a low-cholesterol concentration in the circulating blood stream in most of our cases of peripheral arterial disease that have developed ulcerative lesions of the extremities. In 1 of our cases, this figure is found to be as low as 80 mg. In certain individuals, it would seem that the supply of available cholesterol in the body may be more abundant than in others and in such cases the value of the circulating blood cholesterol does not reach such a low level. Perhaps these are the cases that are more resistant to ulcerative and gangrenous manifestations. It would again appear, therefore, that a low blood cholesterol is not always a necessary finding in cases of generalized arteriosclerosis unless the particular individual is the type which will eventually develop ulcerative lesions. In such cases there appears to be a limited supply of available cholesterol. Coincident with the improvement in the ulcerative lesion, there occurs in all these cases a rise in the blood cholesterol and in the case cited above, where the blood cholesterol at the beginning of the treatment is 80 mg. per 100 cc. of blood, it rises to 230 mg. during the course of treatment. This constitutes practically a rise to 3 times that of the low level. On the other hand, with the recurrence of the symptoms in this particular case, a drop in the blood cholesterol is again noticed to 120 mg. per 100 cc. of blood serum. Another course of intravenous treatments is instituted followed by healing of the ulcerative lesion. The blood cholesterol again rises during the treatment period to 265 mg. in this particular case. This fluctuation in the

blood cholesterol, if properly employed, furnishes a guide, so to speak, as to the indication for resumption of intravenous therapy in a particular case.

It might also be mentioned at this point that the oral administration of these same iodide and chloride preparations was tried for a sufficiently long period of time in each case and proved completely ineffective in all of them. This failure can be explained as due in all probability to two chief reasons: (1) These preparations cannot be tolerated by the patient in sufficiently large doses and over a sufficiently long period of time necessary to have any effect upon the lesions. (2) The poor local circulatory condition present in these ulcerative lesions makes penetration of these preparations very indefinite and highly improbable when administered orally.

Conclusion. Patients with painful ulcerative lesions of the extremities due to peripheral arterial disease, should receive intravenous treatments with sodium iodide or sodium chloride solutions as described above, using the blood cholesterol as an important guide and indication in the administration of such therapy. It is hardly advisable, in the light of our observations, to await the recurrence of ulceration and pain in such cases and inasmuch as our average period of relief is about 8 months, that period of time might be the accepted interval at which time these periodic series of treatments might be instituted, unless indications exist for an earlier resumption of the therapy.

Summary. 1. Cases with painful ulcerative lesions of the extremities due to peripheral arterial disease, were found to have a subnormal or low normal blood cholesterol.

2. After intravenous treatment with 2% sodium iodide prepared in physiologic saline solution, cessation of pain was obtained in all cases.

3. Blood determinations made at repeated intervals during the course of treatment showed a gradual and marked rise in the blood cholesterol content with a subsequent fall.

4. The ulcerative lesions were healed after a period of treatments varying from 4 to 6 weeks.

5. With the recurrence of the peripheral ulcerative lesion a lowering in the blood-cholesterol value was again observed.

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THE HEMATOLOGIC PICTURE OF CHRONIC ULCERATIVE COLITIS; ITS RELATION TO PROGNOSIS AND TREATMENT.

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RECENT hematologic progress has been able sometimes to establish relations between a given hematologic picture and the clinical course of the disease. This work was undertaken to determine what value, if any, the analysis of the hematologic picture of patients who were suffering from chronic ulcerative colitis might have on the prognosis and treatment.

Dameshek,⁷ Davidson and others,⁸ Sours,²⁸ Watkins and Heck,³² Watkins³¹ and others, have written about the etiology, diagnosis and treatment of secondary and hypochromic anemias. The work of Arneth,¹ Cooke and Ponder,⁵ Schilling,²⁷ Mullin and Large,²³ Farley, St. Clair and Reisinger,¹¹ Gorsky,¹³ Eisenberg and Nemens¹⁰ reveals that such information of prognostic value can be obtained from a study of the leukocytes. It was thought that a correlation of these separate studies might enhance our understanding of the hematologic picture of chronic ulcerative colitis. The pathology, bacteriology, local symptoms, and treatment are now well understood by many, but a description and application of information obtained from the hematologic picture have not been reported. This study was undertaken with the well-formulated general principles, which have been outlined by the previously named investigators, as a background. The material for this study consisted of the records of 100 unselected patients who were afflicted with chronic ulcerative colitis; this was augmented by a detailed study of 25 patients who were ill enough to be placed in the hospital.

One of us (Bargen)² has observed for years that patients who have chronic ulcerative colitis and who have not been treated have a markedly lowered value for the hemoglobin. A review of the records of the 125 patients substantiated this observation. There is moderate anemia, and in cases in which the condition is uncomplicated, the number of leukocytes is normal. The values for hemoglobin in this series, which were obtained with the photo-electrometer, ranged from 1.8 gm. to 16.7 gm. per 100 cc. of whole blood (average 11.1 gm.). The number of erythrocytes varied from 1,900,000 to 5,270,000 per cu.mm. In cases in which there was no complication, the number of leukocytes varied from 5000 to 10,000 per

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cu.mm. of blood at the initial examination. The average color index was 0.77. The number of reticulocytes was within normal limits.

These figures were analyzed in many different ways. A study was made of the duration of the disease, the blood count, and hemoglobin when the patients first came under our observation. As a general rule, it can be said that there is no marked relationship between the number of erythrocytes, the value for the hemoglobin and the duration of the disease. The patients who had been ill for only a few months, as a rule, revealed a larger number of erythrocytes than did those who had been ill for longer periods. The patients who had been ill for more than 5 years also tended to have fewer erythrocytes per cu.mm. of blood and a lower value for the hemoglobin than did those who had been ill for a shorter time, but in a large majority of the cases there was little relation between these factors.

These cases also were analyzed to determine the relation between the number of erythrocytes, the value for the hemoglobin and the anatomic extent of the disease. Except for the 1 case of regional chronic ulcerative colitis in which the lesion was confined to the right half of the colon, there was no significant relation of these findings. There was a remarkable constancy between the value for the hemoglobin and the number of erythrocytes; the color index remaining close to 0.77.

It has been demonstrated that the secondary or hypochromic anemias may develop from many different causes,¹⁶ such as acute or chronic hemorrhage, dietary deficiency,^{17, 33} gastro-intestinal disturbances,¹⁵ and chronic sepsis;^{18, 22} finally, there is the idiopathic hypochromic type which is associated with or without achlorhydria.

Chronic ulcerative colitis is unique in that any of the previous factors might play a rôle in the production of the anemia. The chronic hemorrhage is undoubtedly the largest factor in producing anemia. The multitudinous bloody stools each day would be sufficient to produce grave anemia. In addition, there are the limitations in diet that frequently have been imposed on these patients. It is difficult to provide a diet which has a low residue and contains a large amount of iron;³ at best, these diets are comparatively poor in this respect. The altered gastro-intestinal physiology,^{16, 19} particularly the rapid transmission of food through the colon, would lessen the proper utilization and metabolism of foods which contain iron. A striking factor which probably contributes to the cause of the anemia, is the chronic sepsis. Many of these patients have a fever for months, which in itself would be sufficient to produce a moderately severe anemia by the action of the toxin of the specific diplostreptococcus.

Other data usually considered significant in the study of an anemia are unimportant here. The values for gastric acidity are usually within normal limits, the number of reticulocytes is only slightly

increased, the bleeding time and coagulation time are normal, and there apparently is no involvement of the central nervous system.

In cases of uncomplicated chronic ulcerative colitis the number of leukocytes ranges from 5000 to 10,000 per cu.mm. Of the 100 unselected cases there were 23 in which the number of leukocytes was more than 10,000 per cu.mm. At the time of the original examination, the largest number of leukocytes was 17,200. The average number of leukocytes in a case in which there were no complications was 8750 at the time the patient was admitted to the hospital. In every instance in which there was a persistence of more than 10,000, there was a complication of varying severity. There were instances of local complications such as perforation of the intestine or an ischiorectal abscess; or a more remote complication, as acute appendicitis, an infection of the upper part of the respiratory tract, or a flare-up of a quiescent distant focus, such as an abscessed tooth, acute tonsillitis, prostatitis, or iritis. In each case, as soon as the complicating factor was arrested, the number of leukocytes promptly returned to normal.

In some cases in which the patients were under close observation in the hospital, the number of leukocytes decreased to less than 2500 per cu.mm.; in 1 case it decreased to 2300, in another to 2000, and in a third to 1600. Subsequently, the number of leukocytes increased to normal in these cases. This leukopenia occurred in particularly virulent phases of the disease. A sharp decrease in the number of erythrocytes was associated with the leukopenia. As the general and local condition improved, both the number of the erythrocytes and leukocytes increased appreciably.

In general, the differential count was as follows: lymphocytes from 10 to 30%, neutrophils from 60 to 85%, monocytes from 2 to 30%, and eosinophils and basophils from 1 to 2% of the total number of leukocytes. Occasionally, a monocytosis was seen, in which the monocytes comprised 30% of the total number of leukocytes. The previous history and convalescence of these patients were no different from those of patients who disclosed normal leukocyte counts. In those cases in which complications occurred, the percentage of the various leukocytes rose to the expected levels. Neutrophils made up 85 to 95% of the total differential count; lymphocytes 5 to 10%; and monocytes, eosinophils, and basophils 1 to 2%. After the complications subsided, the various cells assumed their previous levels. When a monocytosis of 30% occurred, there was no immaturity or toxicity noted beyond the usual stages which normally are encountered in this disease. There is very little of prognostic or therapeutic value in a study of the differential count without special study of the cells.

Many features of the fundamental nature of chronic ulcerative colitis may be brought out in a detailed study of blood smears. The erythrocytes disclose marked hypochromasia as would be indi-

cated by the low color index. This is uniform and practically all of the erythrocytes share equally in the paucity of the hemoglobin. There also is considerable anisocytosis. A majority of the erythrocytes are slightly smaller than normal erythrocytes.

The leukocytes are of particular interest, and the features can be studied most easily in the neutrophils. These cells reveal many wide variations, but usually conform to a general pattern. The granules are considerably larger than the usual granules, and stain more deeply. A large number of vacuoles may be present. There is a very high percentage of non-filamented cells. Many of the same features can be seen in the monocytes, but they are not so clear cut as they are in the neutrophils and the findings are less obvious. All of these features in the neutrophils indicates a marked shift to the left and a very toxic process.

This investigation of chronic ulcerative colitis has been directed along two other lines. We have been materially aided in this study by the work of Mullin and Large,²³ and by the work of Farley, St. Clair and Reisinger,¹¹ on the filament-non-filament count and on the sedimentation rate. These two tests were studied in the hope that they might indicate whether or not these patients were "cured."

In cases in which chronic ulcerative colitis had not been treated, the filament-non-filament count was greatly altered. We have considered 16 non-filamented cells in each 100 leukocytes as the upper limit of normal. There were as many as 70 non-filamented cells among 100 leukocytes; the average was 17 filamented cells and 44 non-filamented cells at the time the patients were admitted to the hospital. As others have reported, the non-filament count increases and the filament count decreases with unfavorable progress. In 1 of the cases in which there was leukopenia, 78 of 80 neutrophils were non-filamented at the height of the exacerbation; no filamented cells were found for 3 consecutive days. In this disease, considerable favorable or unfavorable progress must be made before any alteration in the filament-non-filament count is noted. When a patient improves, the filament-non-filament count improves gradually, but progressively, until such time as proctoscopic and roentgenologic examination reveals that the patient is "cured" clinically when a normal filament-non-filament count obtains.

The sedimentation rate offers a fairly close corollary to the filament-non-filament count. These two laboratory procedures approximate each other closely in usefulness. We also found that the sedimentation rate was uniform in cases of chronic ulcerative colitis in which the patients had not been treated. There was very little relationship between the sedimentation rate and the extent of involvement or between the sedimentation rate and the duration and the anatomic situation of the disease. Increased sedimentation rates in these cases must be explained in terms of toxemia.²⁰ A sedimentation rate greater than 20 mm. has been considered ab-

normal. Very marked increases in the rate of sedimentation were noted in most of these cases. As in the case of the filament-non-filament count, marked and prolonged symptomatic improvement must take place before the sedimentation rate is appreciably altered. Those patients whom we considered as "cured," by all known criteria had a normal sedimentation rate. In exacerbations, the rate fell to approximately its original level, although the patients did not appear to be as ill as they were when they originally were observed. In contradistinction to the filament-non-filament count, the sedimentation rate shows the effect of extraneous factors more readily. Infections of the upper part of the respiratory tract, acute otitis media, and intestinal perforation, all alter the sedimentation rate greatly. The sedimentation rate promptly returns to its former level as soon as these incidental infections are successfully combated. Our experience would indicate that the sedimentation rate has less value than has the filament-non-filament count.

Comment. Study of the hematologic picture has brought out certain pertinent facts. It is probable that the decrease in the values for the hemoglobin and the decrease in the number of erythrocytes cannot be entirely accounted for on the bases of loss of blood, altered gastro-intestinal physiology, or inadequate diet. This is suggested further by the fact that in cases in which the degree of anemia is equal, the extent of involvement and severity of the disease may be entirely different; in one case the patient may lose much blood by the rectum, and in another case a minimal amount. Recent work by Robscheit-Robbins and Whipple²⁵ has suggested that production of hemoglobin is held in abeyance by severe infection. In cases in which the patients have not been treated, the value for the hemoglobin and the number of erythrocytes are in close relation to the severity of the infection. The reticulocytes are greatly increased; their number remains fairly constant. The metabolism of hemoglobin is probably much slower²⁶ than it is normally; hence the value for the hemoglobin is less than is commensurate with the nearly normal erythrocyte count.

Further evidence that chronic ulcerative colitis is a highly infectious disease is furnished by the observation of a marked shift of the leukocytes to the left, toxic changes in the leukocytes²³ and the greatly increased sedimentation rate.

Schilling,²⁷ Sours,²⁸ Mullin and Large,²³ and Gorsky¹³ believed that, of all the hematologic evidence which indicates that a highly infectious process is in progress, a marked shift of leukocytes to the left is the most reliable and convincing. In chronic ulcerative colitis, this shift to the left is moderate or marked. The non-filamented leukocytes are very numerous and they show such evidence of severe toxic changes as large deeply staining granules, bizarre forms of nuclei and the inclusion of vacuoles.

Harvey and Hamilton¹⁴ maintained that the hematologic picture is a mirror image of the focal process. In a case of uncomplicated

chronic ulcerative colitis in which the patient has not been treated, the number of leukocytes usually is normal. Sours²⁸ has shown that infection stimulates delivery of leukocytes from the bone marrow, and that the more severe the infection, the greater the number of cells which are given out by the marrow. In acute otitis media, Mullin and Large²³ explained the situation by saying that "when increased destruction occurs in infections, an increased demand is placed on the bone marrow and when it is unable to cope with the demand for mature cells, immature forms are poured out." Rarely is there a cell which is more immature than the metamyelocyte. The response to the stimulus is sufficient that further immature cells are not placed in the peripheral circulation. Judging by the high percentage of non-filamented forms, the infection must be very severe, but one must remember that a large region of the body is involved by the disease. A comparison of the following conditions will illustrate the profound toxemia of this infection. In chronic infectious arthritis, according to Steinbrocker and Hartung,²⁹ and Count, 31.5% of the leukocytes are non-filamented cells. In acute gynecologic diseases, 30 to 40% of the leukocytes are non-filamented,²¹ in acute appendicitis, 30 to 50%.

When the demand for leukocytes suddenly becomes acute, as the result of increased toxicity, a leukopenia may develop. This is shown in the cases in which there were less than 2500 leukocytes in each cu.mm. of blood. Synchronous with the sharp decrease in the total number of leukocytes, the number of filamented cells may decrease to zero. Along with the sharp decrease in the number of leukocytes was a corresponding decrease in the number of erythrocytes and values for the hemoglobin. As the general condition improved, the number of filamented and non-filamented cells returned to the average for this disease. Schilling,²⁷ Sours,²⁸ Gorsky,¹³ and Markowitz²¹ interpreted the events as a temporary paralysis of the bone marrow with greatly increased peripheral destruction of cells. These cases correspond to Group 4 of Schilling's²⁷ classification, in which there is irritation of the bone marrow by the toxic process, and a resulting leukocytic response.

Another link in the evidence that chronic ulcerative colitis is a highly infectious disease, is the result obtained from a study of the sedimentation rate of the erythrocytes.^{6, 20, 24, 33} Other conditions also may produce or increase in the sedimentation rate. Considering the rate of sedimentation which was obtained in cases of chronic ulcerative colitis in which the patients had not been treated, the test indicates a much more virulent and widespread infection than is present in the other diseases which have been mentioned. We believe this, along with the associated change in the leukocytes and erythrocytes, is significant.

In those cases of chronic ulcerative colitis in which clinical, proctoscopic, and roentgenologic examination indicated that the patients were cured, the number of leukocytes, the filament-non-

filament counts, and the sedimentation rates were normal. A normal sedimentation rate and a normal filament-non-filament count are not encountered in cases in which there is any sign of activity of the disease, as blood in the stools, tenderness over the colon, proctoscopic evidence of ulceration, or roentgenologic evidence of "feathery edges" of the colon. Many times, the problem arises as to the advisability of allowing a patient to relax his vigilance in the treatment of this prolonged disease, and it is of great importance to be able to substantiate an opinion of the absence of infection by the evidence offered by the sedimentation rate and the filament-non-filament count. The same criteria are used in the treatment and prognosis of such diseases as tuberculosis, acute rheumatic fever,¹⁹ chronic infectious arthritis,⁴ and pelvic infections.²¹ In chronic ulcerative colitis, an additional aid is offered in making the differential diagnosis of symptoms which are the result of activity of the disease and those which are the result of narrowing of the rectum from scar tissue. In the latter instance, if other factors which affect the tests are controlled, the results of the filament-non-filament count will be well within the normal range. The results of these two simple procedures frequently govern the institution of surgical intervention, the omission of active treatment, and the relaxation of the constant vigilance.

This study also includes the rôle of the hemoglobin and the erythrocytes in the ultimate outcome of the disease. There is no gross relationship between the value for the hemoglobin, the number of erythrocytes, and the duration, extent, or anatomic situation of the disease. If, however, one separates the cases in which the value for the hemoglobin or erythrocytes is normal and those in which these values are subnormal, there will be a marked disparity in the duration of the disease. The average duration in the cases in which the value for the hemoglobin was normal was 1.3 years, as compared with 3 years in those cases in which the value for the hemoglobin was decreased.

It is a common procedure to base prognosis on the value for the hemoglobin and the number of erythrocytes.⁹ In attempting to establish the relationship between the value for the hemoglobin and the duration of treatment, our attention was directed to ways and means of increasing the amount of hemoglobin and the number of erythrocytes. The standard treatment of hypochromic anemia is the administration of proper doses of some preparations which contains iron.^{7, 8, 9, 12, 15, 17, 30, 31, 32} On account of the hyperirritability of the colon in cases of chronic ulcerative colitis, it is not always possible to administer therapeutic doses of iron without increasing the diarrhea. Reduced iron, ferric citrate, iron and ammonium citrate, pills of ferrous carbonate (Blaud's pills), ferric chloride and other similar preparations are administered with only fair success. In the cases in which it was possible to administer one of the drugs

in sufficient amount, definite and prompt improvement was noted in the general condition and in the local symptoms. Another method of increasing hemoglobin and erythrocytes is to resort to blood transfusions. Prior to this study, transfusions of blood often had been administered in cases in which there was a decrease in the amount of hemoglobin and in the number of erythrocytes. It would seem to be a good practice to administer transfusions of blood periodically until both the amount of hemoglobin and the number of erythrocytes are approximately normal in cases in which patients do not tolerate iron when it is administered orally. It is a well-established practice to administer repeated transfusions of 200 to 250 cc. of blood, rather than the usual 500 cc. If the latter amount is administered, the loss of blood through the rectum is greatly increased and only a small part of the original transfusion is utilized. Transfusions of 200 to 250 cc. usually are well utilized and do not cause any disturbance. Occasionally, amounts as small as 100 cc. are indicated. After the amount of hemoglobin and the number of erythrocytes have returned to normal, it frequently is possible to administer one of the preparations of iron in sufficient amounts in order to maintain the normal amount of hemoglobin and the normal number of erythrocytes. Those patients who receive transfusions until these constituents of the blood are normal, experience a sharp gain in general well-being and a secondary improvement in the intestinal disturbance. These aids are not of primary importance but are valuable additions to the treatment which has been outlined by one of us (Bargen).²

As a control, we studied a group of cases of amebic dysentery and a group of cases in which the diagnosis was irritable colon and so-called "colitis." In cases of amebic dysentery, the value for the hemoglobin and the number of erythrocytes was normal. The number of leukocytes was essentially the same as it was in the cases of chronic ulcerative colitis. In cases of uncomplicated amebic dysentery the number of leukocytes was normal, but the non-filamented cells were increased, the average being 47% of the total leukocytes. The sedimentation rate also was increased.

In cases of irritable colon, the value for the hemoglobin and the number of erythrocytes were entirely within normal limits. Enumeration of the leukocytes and differential counts did not reveal any abnormality. The sedimentation rate and the filament-non-filament counts were normal.

While we were engaged in this study, a patient who had primary hypochromic anemia⁸ with normal gastric acidity and marked diarrhea was under our observation. The number of leukocytes ranged from 3500 to 4000 per cu.mm. of blood, but a normal filament-non-filament count obtained, and the sedimentation rate also was within the normal range.

Summary. Chronic ulcerative colitis reveals the picture usually seen in severe infectious processes.

Transfusions of 200 to 250 cc. of blood appear to be the most efficacious means of increasing the amount of hemoglobin and the number of erythrocytes. A marked subjective and objective improvement was noted when these constituents of the blood approached normal.

Administration of some preparation of iron, in therapeutic dosage, is necessary to maintain the normal amount of hemoglobin and the normal number of erythrocytes.

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FURTHER OBSERVATIONS ON PARENTERAL LIVER EXTRACT THERAPY IN PNEUMONIA.

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THE use of parenteral liver extract in 2 cases of streptococcus pneumonia has been previously reported by one of us.⁹ In this

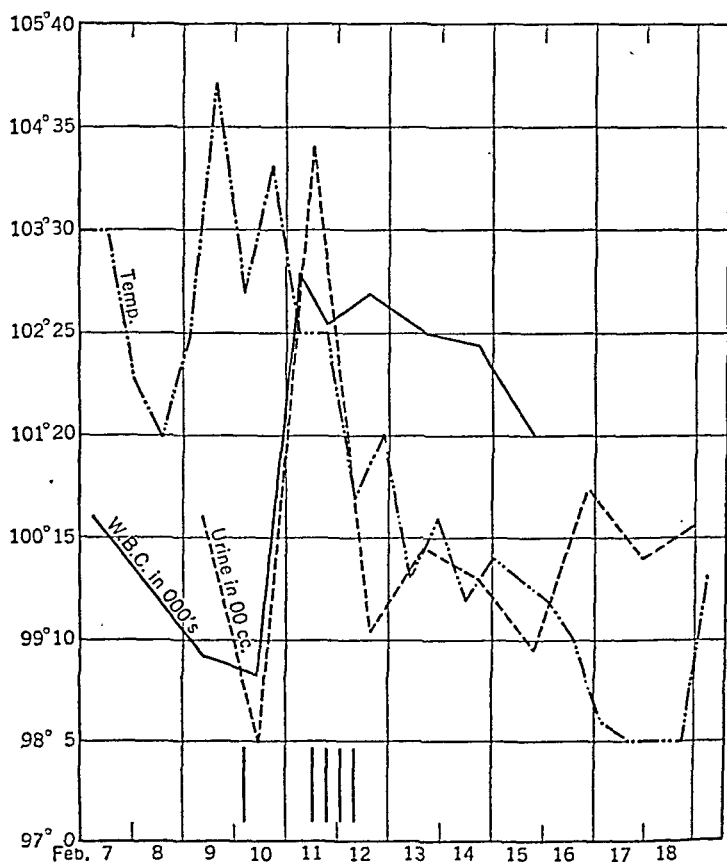
paper, the results obtained in 28 additional cases treated with parenteral liver extract are reported, making a total of 30. These include 8 streptococcus pneumonias, 1 staphylococcus, and in the remainder the pneumonococcus was most frequently found to be the causative organism. Five of the 30 cases died, a mortality of 16.7%. Five cases were treated in their homes; the other 25 were private and ward patients in the Meriden Hospital. Two children are in the series. All were cases of pneumonia with a leukopenia or falling leukocyte count; 3 were pneumonias occurring in the course of a streptococcus septicemia and 2 of these septicemias were the only cases to receive serum. They were given intravenously polyvalent antistreptococcic serum. No antipneumococcic serum was used.

A leukocyte count of over 15,000 was present in only 8 cases at the beginning of treatment; the rest were under 15,000. Cases of pneumonia with a high sustained leukocyte count were not treated with parenteral liver and are not included in this discussion. In the group which was given liver extract therapy the prognosis was not good from the point of view of clinical status and leukocytosis. This was demonstrated by Middleton and Gibbon⁴ who studied 164 cases of pneumonia in a hospital practice and found that a leukocyte count above 20,000 indicated a much better prognosis than a count below this level. Fleming² studied at the Glasgow Infirmary the leukocytosis in typed lobar pneumonia, serum treated. "Of the total 147 cases (with 21 deaths) 30 failed to exceed 10,000 cells, and this number contained 33% of the total deaths. The 47 cases which had counts of 15,000 and under included 62% of the total deaths. For this reason it has been found useful to regard a count of 15,000 or more as an 'adequate' leukocytosis during the acute illness." His findings also indicated the age of the individual governed the prognosis. A leukopenia in a patient over 40 years of age indicates an unfavorable prognosis.

Insufficiency of the bone marrow has been discussed recently by Middleton and Meyer.⁵ They believe a leukopenia may reflect a partial leukogenetic failure of the bone marrow and that bone marrow may be stimulated by treatment, probably by chemotaxis. Following their line of thought, it seems possible that pneumonia may more often occur in individuals whose leukogenetic function is below normal than in persons whose leukogenetic functions are normal. If this is the case, it seems rational to use some therapy that would stimulate the bone marrow activity.

When Murphy⁷ showed that liver extract stimulated the bone marrow of pernicious anemia to greater erythropoietic activity, he also called attention to the fact that leukopoiesis was stimulated. Powers, Murphy, and Humphreys,⁸ in a study of the effect on normal individuals of parenteral liver extract, found a definite increase in the white blood cell count in 21 normal subjects. There was a 94%

increase in ambulatory persons and a 72% increase in recumbent persons. The peak of the leukocyte count was reached in about 7 hours after the injection, then the count slowly returned to normal. Meyer, Middleton, and Thewlis³ using parenteral liver found an increase of leukocytes in 4 cases.



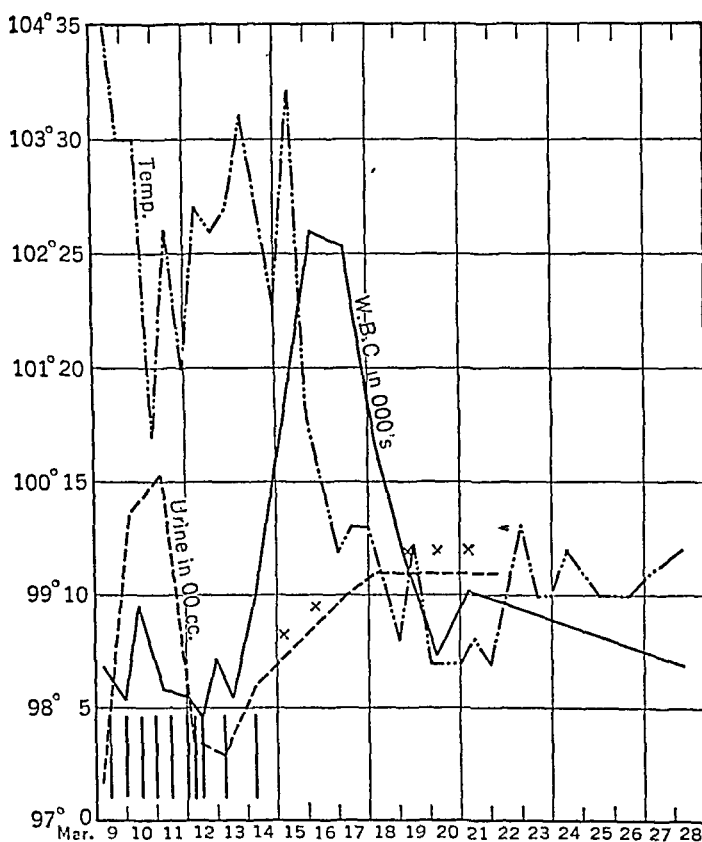
GRAPH 1.—LEUKOCYTE COUNT, TEMPERATURE, AND URINE OF CASE 1.

The straight line is the leukocyte count in thousands; the dotted line the temperature taken in the morning and in the evening; the broken line the urine in hundred cc.; the vertical lines are injections equivalent to 150 gm. of fresh liver.

Thus, the rationale of the use of parenteral liver extract therapy may be summarized as follows: 1, Parenteral liver extract stimulates leukocytosis; 2, in some pneumonias the blood picture is characterized by a relative leukopenia or a falling white blood count; 3, these cases offer a more unfavorable prognosis; 4, therefore, parenteral liver extract given to these cases should stimulate leukocytosis and as a secondary effect improve the clinical picture and progress.

Method of Treatment. The concentrated liver extract was injected intramuscularly in varying amounts, depending on the severity of the infection and the leukopenia developing during the course of the disease. The

injections were made deep into the muscles in the buttock and deltoid regions. The average amount was 6 cc. a day. In 1 case 16 cc., the equivalent of 800 gm. of fresh liver, was given during 24 hours with a very satisfactory result. Lately we have given by injection 2 to 4 cc. of liver extract using extract equivalent to 100 gm. of fresh liver every 6 to 8 hours. It has been shown⁸ that the count reaches its peak in 7 hours after the injection. A majority of the patients were kept in oxygen tents as long as dyspnea and cyanosis were present. Expectorants, such as ammonium chloride, were given in gr. 10 doses every 2 to 4 hours. Morphine and codeine were given for severe pleural pains. In case of beginning heart failure during the time of the crisis, digalen 20 drops and strychnine gr. 1/40 with or without atropine sulphate gr. 1/100 were given hypodermically at 4-hour intervals 3 or 4 times. No digitalis was given at any other time and no cases were digitalized. An effort was made to keep the fluid intake between 3000 and 4000 cc. daily. Liquid and soft diet were given in small amounts frequently. Whiskey was prescribed in small amounts for elderly persons. Quiet and rest were particularly sought, and several of the patients had the benefit of private nursing care. No purgatives were allowed. If constipation became marked, normal saline enemas were given.



GRAPH 2.—LEUKOCYTE COUNT, TEMPERATURE, AND URINE OF CASE 24.

The straight line is the leukocyte count in thousands; the dotted line the temperature taken in the morning and in the evening; the broken line the urine in hundred cc.; the days marked x it was involuntary; the vertical lines are injections equivalent to 200 gm. of fresh liver.

Results of Treatment. There was an approximate increase in leukocyte count of 70% and the range was from 6 to 239% increase.

This is based on counts taken in some cases twice a day and can only be approximate because it has been shown⁸ that the count will vary from hour to hour, and after an injection of concentrated liver extract the leukocyte count gradually rises for 7 hours, then gradually falls. All but 6 cases responded by an increase in leukocyte count. There was a daily drop in the white blood count until liver extract treatment was started. This is usually considered a very ominous sign. One of the cases which had a count above 15,000 was a case of Type III pneumococcus in which the count was 22,400 at the beginning of liver injections. The count rose to 30,400 and the patient made a complete recovery. Several patients showed a marked increase in urinary output the day after parenteral liver was given, confirming the observation made in the first case studied⁹ and apparently establishing the fact that parenteral liver extract stimulates the kidneys to greater urinary output. No anaphylactic reactions occurred either locally or generally. Graph 1 gives the reaction that resulted a few hours after liver extract was given. Graph 2 gives the rise that occurred in leukocytes after 6 days of liver injections. This appeared to be a delayed reaction. The count averaged 5000 for 6 days, then in 3 days rose to 25,000. Recovery then took place.

Fatal Cases. The first instance in which death occurred was a woman, aged 38, who died on the tenth hospital day and who had been ill 4 days before entering the hospital. An autopsy showed many fine abscess cavities throughout both lungs from which staphylococci were cultured. This was regarded as a staphylococcus pneumonia although it may have been a mixed infection like those reported by Finland,¹ who found that 133 out of 2000 indicated a primary pneumococcus with a staphylococcus or streptococcus infection superimposed. The second case to die was a chronic alcoholic who had been ill 2 weeks, beginning with a marked diarrhea and fever followed by jaundice. He died from an apparently terminal pneumonia. The liver extract was started the day before death with no improvement and a very slight rise in leukocytes, then a moderate fall before death. The third case to succumb was a man of 32 who had a Type III pneumococcus infection. His white blood count fell from 18,000 to 2000 in 3 days and he failed rapidly and died on the fifth day of his illness despite liver therapy. The fourth case to die was one of streptococcus septicemia following a very acute pharyngitis, cellulitis of the right arm, and lobar pneumonia at the base of the left lung. Liver extract was given daily for 5 days. The leukocyte count remained between 4000 and 9000. On the seventh day it rose to 17,600 and on the eighth to 26,000. The temperature then subsided. The abscess in the right arm was incised. The patient did very well and was out of bed a short time on the nineteenth and twentieth days. During the evening of the twentieth day the patient died suddenly of a pulmonary embolus.

TABLE 1.—CLINICAL DATA ON 30 CASES OF PNEUMONIA.

Case No.	Sex.	Date.	Age (yrs.).	Organism.	W. B. C. (thous.)			Urine (100 cc.).			Liver extract (gm.).	Remarks.	Recovered or expired.
					(1)	(2)	(3)						
1*	M.	1934 2/10	45	Strep.	8.2 (See Graph 1)	27.8	26.8	16.0	5.0	34.0	800	L. U. Lobe. Marked toxemia. Delirious	Rec.
2*	F.	5/22	38	Staph.	14.6	15.2	18.0	9.0	23.0	12.0	1250	L. U. Lobe. 2 neg. and 1 pos. blood cultures. Ill 12 days	Exp.
3*	F.	7/18	21	Strep.	5.2	7.2	12.2	3.0	6.0	10.0	1400	L. U. Lobe. Yellow sputum. Good recovery	Rec.
4	M.	9/8	40	Strep.	8.2	12.2	14.0	950	R. L. Lobe. Pleurisy but no effusion. Treated at home. Bright red sputum	Rec.
5*	F.	9/18	19	II	8.2	8.0	8.8	10.5	10.0	10.0	600	L. L. Lobe. Pleurisy but no effusion. Very ill after pneumothorax	Rec.
6*	F.	12/19	45	8.2	11.2	9.4	13.5	18.0	20.0	1100	L. L. Lobe. Long convalescence	Rec.
7*	M.	12/27	22	Strep.	5.8	6.4	9.0	22.0	22.5	27.5	800	L. L. Lobe. Not very toxic	Rec.
8*	F.	12/28	62	Strep.	8.4	15.2	21.8	3.0	14.5	25.0	600	R. L. Lobe. Not very toxic. Slow recovery	Rec.
9*	M.	12/30	35	III	19.2	19.8	2.0†	7.0	7.0	12.8	1700	Left lung. Pos. blood culture. Rapidly fatal	Exp.
10*	F.	12/30	32	Strep.	9.6	13.4	15.0	6.0	17.9	9.5	450	R. L. Lobe. Prolonged convalescence	Rec.
11*	M.	1935 1/2	14	12.6	8.0	12.4	8.5	15.5	10.5	1050	R. L. Lobe. Light attack. Good recovery	Rec.
12	M.	1/5	42	8.0	6.6	15.0	4.8	31.5	20.0	1000	L. L. Lobe. Pleurisy but no effusion. Treated at home. Very ill few days	Rec.
13	M.	1/6	56	8.0	9.0	7.8	600	Bronchopneumonia following coronary attack	Rec.
14*	F.	2/15	45	III	22.4	24.8	30.4	11.0	18.5	12.0	500	Bronchopneumonia. Not very toxic. Good recovery	Rec.
15*	M.	2/28	40	Neg. I, II, III	14.8	17.8	26.3	850	L. L. Lobe. Second attack pleurisy—no empyema. First had empyema	Rec.
16*	M.	3/22	45	13.6	13.0	10.6	900	R. U. Lobe. Chronic alcoholic. Liver given last 24 hours	Exp.
17*	F.	10/12	59	Strep.	13.8	15.8	24.2	15.7	17.0	11.0	900	R. L. Lobe. 1 neg. blood culture. Good recovery. 6 days	Rec.
18*	F.	10/26	72	4.6	9.0	12.6	6.5	10.5	6.5	900	R. L. Lobe. Treated at home several days	Rec.
19	F.	11/18	69	No sputum	3.4	3.2	7.6	4150	L. L. Lobe. Quite toxic. Pernicious anemia. R. B. C. 1,520,000	Rec.
20*	F.	1836 1/10	50	10.8	20.8	18.0	200	R. L. Lobe. Influenza type. Treated at home	Rec.
21	M.	2/20	54	16.6	16.5	20.0	250	R. L. Lobe. Treated at home. Good recovery	Rec.
22*	F.	2/24	75	Strep.	20.0	20.0	25.0	9.0	14.5	11.5	1550	R. L. Lobe. 1 pos. 12 hr. blood culture. Complication of infected foot and septicemia	Rec.
23*	F.	3/3	43	Strep.	17.8	17.4	19.0	8.0	10.0	13.0	1000	L. L. Lobe. 2 neg. blood cultures. Pleurisy but no effusion. Streptococcus septicemia. Died of embolus on 25th day	Exp.
24*	F.	3/9	75	III	6.8 (See Graph 2)	5.6	26.0	Involuntary			2000	Both bases. 2 neg. blood cultures. Very excellent recovery. Diabetes mellitus, insulin given. Blood sugar 375 mg.	Rec.
25	F.	3/14	63	14.0	10.6	14.0	700	L. L. Lobe. Coronary attack. Treated at home	Rec.
26*	M.	3/28	36	Strep.	11.8	23.4	19.8	12.0	15.7	13.5	2900	Infarct both lungs. Pos. blood culture. Streptococcus septicemia. Pneumonia complication of infection. Very ill. Good recovery	Rec.
27*	F.	3/31	75	IV	16.4	12.2	14.4	9.5	11.7	20.5	2800	Bilateral pneumonia. Neg. blood culture. Good recovery	Rec.
28	F.	4/26	33	XXI	3.8	4.6	5.2	3.6	3.6	4.0	2700	R. L. Lobe. Neg. blood culture. Terminal pneumonia. Malignant hypertension	Exp.
29	M.	5/4	45	30.0	25.2	24.4	1700	L. L. Lobe. Very ill at home 5 days before hospitalization. Severe epistaxis	Rec.
30	M.	5/5	57	V	23.0	20.6	13.0	1200	L. U. Lobe. Lobar 4 days' duration on entrance. Blood sugar 250 mg.	Rec.

* Indicates that the clinical diagnosis was confirmed by Roentgen ray.

† Last count before death.

(1) under W. B. C. is the count before liver injection;

(2) is the count 7 hours after the injection, or, where that was not available, the next day;

(3) is the highest count during the liver therapy.

The fifth fatality was a single woman, aged 42. She had been suffering from a malignant hypertension for 5 years and her pneumonia was a terminal condition. She was ill 6 days. She failed very rapidly. Her blood cholesterol was below 100 mg. before death. This case was included in the series because she was given the parenteral liver extract.

Discussion. We are well aware that a group of 30 cases of pneumonia are all too few from which to draw any definite conclusion, and we do not wish to compare the parenteral liver treatment with the many other treatments of pneumonia. We simply wish to record our experiences. As we have used this treatment over the last 3 years, we have continued to be impressed with its possibilities.

Our mortality rate of 17% appears favorable. In this same hospital there was a mortality of 33.5% in all pneumonias during 1933.⁶ The 5 cases that succumbed were very ill and after close study we doubt if any method of treatment would have been successful. Twenty-two of the group were 40 and over, ranging up to 75 years; 2 of this group died, giving a mortality rate of 9%. One of these was the case that suffered a sudden pulmonary embolus on the twenty-second day.

The parenteral liver treatment is safe, simple to give, very economical, free from serum sickness and anaphylactic reactions. The only objection is the pain that occurs at the site of the injection. This is moderate and of short duration.

After studying the blood counts in pneumonia one cannot help but be impressed by the poor reaction of the bone marrow in a considerable percentage of pneumonias and by the falling white cell counts that occur in many of the critically ill patients. Does "insufficiency of the bone marrow" as put forth by Middleton⁵ predispose these individuals to pneumonia?

Conclusions. 1. Thirty cases of pneumonia treated with parenteral liver resulted in recovery in 83%.

2. The use of parenteral liver extract was accompanied by a significant rise in the white blood count in all but 2 cases and clinical improvement occurred simultaneously.

3. In the great majority of the cases there was an increased urinary output following the injection of parenteral liver.

4. The treatment is safe, economical, and free from serum sickness. It causes moderate pain at the site of injection.

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THE USE OF P-AMINO BENZENESULPHONAMIDE IN TYPE 3 PNEUMOCOCCUS PNEUMONIA.

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ALTHOUGH Domagk² reported that the therapeutic effect of Prontosil* in animals was strictly specific for streptococcus and staphylococcus, but ineffective against pneumococci, Hörlein⁴ has obtained contradictory results with the latter, some being negative, and others positive. Inasmuch as no experimental data were given, a well considered opinion is impossible. No mention is made of tests with the para-amino compound.

The favorable outcome of the experiments of Rosenthal⁵ on the influence of p-aminobenzenesulphonamide on Type 1, 2 and 3 pneumococcal infections in mice, and of the studies of Cooper, Gross and Mellon¹ and of Gross and Cooper³ on Type 3 infections in white mice and white rats, appeared to justify a study of the influence of this therapeutic agent on patients suffering from lobar pneumonia due to the Type 3 pneumococcus.

Opportunity for such a study was presented by the unusually high incidence of Type 3 pneumonia infections occurring in the Pittsburgh area during the present pneumonia season.†

According to our records, Type 3 cases began to appear early in the season (September) and came to a peak with 11 cases in January. After this period, which also marked the height of the influenzal infections, the number diminished during February (2 cases) and

* Three sulphonamide compounds have been used in this form of chemotherapy: (1) Prontosil I, which is the hydrochloride of 4'-sulphamido-2, 4-diaminoazobenzol; (2) Prontosil II (or S) is the di-sodium salt of 4'-sulphonamide-phenol-azo-1-oxy-7-acetyl-amino-naphthalin-3, 6-disulphurous acid; (3) para-amino-benzenesulphonamide. These compounds have been introduced commercially under various trade names.

† That the higher incidence of Type 3 pneumonia during the present season has not been peculiar to Pittsburgh alone is demonstrated by information received from hospitals in New York City, Albany, Buffalo, Cleveland and Philadelphia. On the other hand, it should be noted that, in some of the cases here reported, we may not have been dealing with wholly typical Type 3 lobar pneumonia, but a type of infection perhaps comparable with some of the influenzal pneumonias that occurred during the 1917-1918 influenza epidemic. This probability is enhanced by the fact that the majority of the Type 3 cases here reported occurred during the recent influenza-like epidemic in Pittsburgh; and that the number of Type 3 cases diminished rapidly as the wave of influenzal infection subsided. Moreover, Type 3 pneumococci were observed in the sputums of a few patients in which characteristic pneumonia did not develop, although no Type 3 organisms were found in cultures from the throats of 15 influenza patients.

March (2 cases). This rather remarkable increase in Type 3 cases was not only actual, but relative; for, from the beginning of the pneumonia season and continuing through January, the number of Type 3 cases under observation exceeded the number of Type 1 and 2 cases combined. At the time of writing (March), the number of Type 1 and 2 cases is again rapidly mounting, and this new trend is accompanied by a corresponding decrease (both actual and relative) in the number of Type 3 infections.

In this paper there are reported 19 cases of Type 3 pneumonia. Of these, 9 were treated with p-aminobenzenesulphonamide (Prontylin) and 10 received no special form of treatment. These cases occurred from September to March, inclusive; and the majority were under observation during January. By late February and in March, Type 3 cases were comparatively rare.

The typings were done by the Neufeld method from sputum, and from positive blood cultures when available. In view of the cross-reactions that often occur between Types 3 and 8, a special effort was made to rule out Type 8 infections in the present series. In only 1 case (M. G., treated) was a difficulty experienced in distinguishing between these 2 serologic types. One piece of evidence supporting the authenticity of the type-diagnoses lies in the circumstance that, during the period of study, there occurred in this hospital 6 cases of Type 8 pneumonia, all except 1 of which recovered. Their differentiation from Type 3 presented no special difficulty. Type 4, 5, 6 and 7 cases manifested about normal incidence during this period.

Treatment consisted of the oral administration of p-aminobenzenesulphonamide (Prontylin) which, in a few cases, was augmented by intramuscular injections of Prontosil. Owing to the late arrival in the hospital of some of the patients, the first administration of sulphonamide was sometimes considerably delayed.

With reference to predisposing factors, complications, age, etc., there was a general similarity between the 2 groups (treated and untreated), although these factors were somewhat more favorable to the treated group. For example, in the untreated group there was 1 patient with an asthmatic condition, 1 with a slight myocarditis and 1 that was an alcoholic; these were among the patients that died. In the treated group, on the other hand, in 1 patient the Type 3 infection was superimposed upon a Type 7 pneumonia; and this patient recovered. Positive blood cultures were obtained from 2 patients of the untreated group and from 1 patient in the treated group; all 3 patients died.

While a bacteremia is now generally recognized as of serious prognostic import, what many regard as the *critical* or recovery level (30 colonies per cc.) may vary from season to season within wide limits. In this connection the results of Dr. George H. Robinson, Bacteriologist of the Allegheny General Hospital, seem pertinent.

Six of Dr. Robinson's 7 fatal Type 3 bacteremic cases were well

within the critical level—4 of these being essentially negative (one colony or less per 10 cc. of blood). Yet they all died in this influenza season⁸ While the private nature of many of our cases made it impracticable to do serial blood cultures, the conditioned nature of this criterion would in any event make necessary the treatment of larger numbers of cases in order to assess properly the value of the drug.

As to age incidence, the situation slightly favored the treated group. The average age of the treated patients was 44.4 years; that of the untreated, 49.2 years. In the treated group the only 2 patients that died were the 2 oldest (60, 67). In the untreated group the only patients that recovered were (with one exception) the 2 youngest (31, 39), the exception being an alcoholic (36). In both groups, age was clearly a modifying factor; but the influence of increased age as a factor militating against survival appeared to be less marked in the treated than in the untreated group.

TABLE 1.—UNTREATED HOSPITAL CASES.

Case No.	Initials.	Sex.	Age, yrs.	Onset.	Entered hosp.	Remarks.	Died.
1	T. C.	M	49	1/10/37	1/14/37	Lobar pneumonia, Type 3; left base; following influenza; blood culture for pneumococcus Type 3 positive	1/14/37
2	R. N.	M	64	11/30/36	12/ 8/36	Bilateral lobar pneumonia, Type 3; no complicating features; blood culture negative	12/ 8/36
3	M. E.	F	60	11/16/36	11/23/36	Bilateral lobar pneumonia, Type 3; asthmatic condition present; no blood culture taken	11/25/36
4	A. E.	F	53	10/ 4/36	10/ 5/36	Bilateral lobar pneumonia, Type 3; blood culture negative; no complicating conditions	10/ 7/36
5	J. M.	M	42	9/12/36	9/15/36	Bronchopneumonia, Type 3; myocarditis present; no blood culture taken	9/16/36
6*	D. P.	M	39	11/26/36	12/ 1/36†	Bronchial pneumonia, Type 3; no complications; no blood culture taken	Recovered.
7*	W. S.	M	31	Prev. to 11/29/36	11/29/36†	Lobar pneumonia, Type 3; right middle lobe; no complications; no blood culture taken	Recovered.
8*	M. S.	F	54	1/ 7/37	Treated at home.	Double lobar pneumonia, Type 3; no complications; no blood culture taken	6th day of disease.
9	J. McK.	M	36	Prev. to 1/15/37	1/16/37	Bilateral lobar pneumonia, Type 3; alcoholism; blood culture negative (Frantylin begun 1/16/37; discontinued after 25 gr.).	1/18/37
10	D. McC.	F	64	?	3/12/37	Lobar pneumonia, left base; blood culture positive 3/12/37; no complications	3/13/37

* Outside cases.

† Seen by physician.

While it is true that the average delay in entering the hospital after onset was slightly greater in the case of the untreated group (4.2 days) than in the treated group (2.6 days), it is not believed that this was a factor of great significance. Indeed, the 2 cases that recovered in the untreated groups were not hospital cases. Delay in entering the hospital may have had an influence in 2 or 3 cases (untreated group) that did not enter until the eighth or ninth day of illness, and died soon afterward. These patients, however, also happened to be the oldest of the group.

Tables 1 and 2 present briefly the circumstances surrounding each observed case in both groups:

These observations, together with data compiled on 33 additional cases of alleged Type 3 pneumonia occurring in Pittsburgh during the same period, are summarized in Table 3:

Summary and Conclusions. It has been shown that in a group of 9 cases of Type 3 pneumonia treated with p-aminobenzenesulphonamide, 7 patients recovered and 2 died. In a corresponding group of 10 patients observed approximately during the same period, but not receiving sulphonamide treatment, 2 patients recovered and 8 died. In a group of 33 cases in the Pittsburgh area, but not

TABLE 2.—TREATED HOSPITAL CASES.

Case No.	Initials.	Sex.	Age, yrs.	Onset.	Entered hosp.	Remarks.	Died.
11	C. J.	M	30	1/ 6/37	1/ 9/27	Lobar pneumonia, Type 3; left side with pleural effusions; blood culture negative; Inf. started as Type 7 pneumonia; recovery after administration of Type 5-7 pneumococcus serum; Type 3 infection superimposed on 1/18/37; Prontylin from 1/19/37 (5 gr. each 2 hours) to 1/27/37; few intramuscular injections of Prontosil given	Recovered. 1/31/37
12	J. McA.	M	67	1/15/37 or before	1/16/37	Lobar pneumonia, Type 3, right base; no complications; blood culture positive for Type 3 pneumococcus; Prontylin by mouth 1/21/37 (10 gr. each 2 to 4 hours); discontinued 1/27/37	1/24/37
13	T. S.	F	60	About 1/16/37	1/19/37	Bilateral lobar pneumonia, Type 3; blood culture negative 1/21/37; no complications; Prontylin by mouth 1/21/37 and 1/22/37 (5-10 gr. every 2 hours)	Recovered.
14	L. A.	F	54	1/17/37	1/24/37	Lobar pneumonia, Type 3; right upper lobe; blood culture not taken; no complications; Prontylin 1/24/37 (10 gr. every 3 hours); discontinued 1/26/37	Recovered.
15	C. S.	F	46	1/29/37	1/31/37	Unilateral lobar pneumonia, Type 3; no complications; no blood culture taken; Prontylin by mouth 2/1/37 (5 gr. every 2 hours); discontinued 2/10/37	Recovered.
16	M. G.	M	33	About 2/15/37	2/16/37	Lobar pneumonia, Type 3; no complications; blood culture negative 2/16/37; Prontylin soon after diagnosis (10 gr. every 2 to 3 hours) by mouth; also received few intramuscular injections of Prontosil; treatment discontinued 2/24/37	Recovered.
17*	M. McC.	F	32	1/27/37	1/27/37†	Lobar pneumonia, Type 3; right side and lower lobe; no blood culture; mouth gradually decreasing doses (40 to 15 gr. daily)	Recovered.
18*	M. P.	F	40	Prev. to 1/20/37	1/20/37†	Lobar pneumonia, Type 3; no blood culture; Prontylin (exact dates uncertain) (30 to 50 gr. per day) continued for 4 or 5 days; few intramuscular injections of Prontosil	Recovered.
19	S. B.	F	38	1/25/37	1/26/37	Lobar pneumonia, Type 3; right middle	Recovered.

* Outside cases.

† Seen by physician.

TABLE 3.—RESULTS OF TREATMENT IN TYPE 3 PNEUMONIA.

Group.	Cases treated.				Cases untreated.				
	Cases.	No. died.	% died.	No. recov.	% recov.	Cases.	No. died.	% died.	No. recov.
Reported series	9	2	22	7	78	10	8	80	2
Other cases	33	24	73	9
Totals	43	32	74	11

under our direct observation, 9 patients recovered and 24 died. The mortality rate for all untreated patients was 74%; that for the treated patients, 22%.

Despite the fact that the number of treated Type 3 cases here reported is small, and that the treated group was somewhat favored

by the factors of age incidence and by the absence of significant complicating features, the nature of the difference in relative mortality in the treated and untreated groups appears to justify continued application of the treatment of Type 3 pneumonias by p-aminobenzenesulphonamide until a sufficient number of cases have been accumulated to justify a final judgment as to the efficacy of this mode of therapy. Particularly is this to be emphasized in light of circumstances which made it impracticable to carry out serial blood culture studies.

SUPPLEMENTARY NOTE.—Since going to press 4 additional cases have been treated. Two of these received the treatment within 48 hours after the onset and made a prompt recovery. The other two died in about 12 hours after entering the hospital, thus precluding an effective administration of the drug.

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SPONTANEOUS HEMOPNEUMOTHORAX.

REPORT OF THREE CASES WITH A REVIEW OF THE LITERATURE.

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ALTHOUGH traumatic hemopneumothorax occurs fairly frequently as a complication of crushing or penetrating wounds of the chest and is discussed in standard treatises on thoracic surgery, spontaneous hemopneumothorax is much less common and one finds few references to it. However, it is probably more common than the recorded cases would indicate. Many doctors hesitate to report a single case, or do not realize the apparent infrequency of this condition. For example, when Wilson³⁷ read his paper reporting 2 cases, the discussion brought to light 7 others, previously unreported. It is possible that in some instances the hemorrhagic nature of the fluid is not recognized, and a diagnosis is made of spontaneous pneumothorax with effusion. In fact, spontaneous hemopneumothorax undoubtedly represents merely a spontaneous pneumothorax in which unusual conditions are present to give rise to a greater or lesser amount of bleeding into the pleural cavity. Unless thoracentesis becomes necessary for the relief of dyspnea, or unless signs of internal hemorrhage become conspicuous, an exploratory puncture may never be done. I wish to present briefly the records of 3 cases, discuss the etiology and treatment, and call attention to other recorded cases (Table 1).

TABLE 1.—ANALYSIS OF RECORDED CASES OF SPONTANEOUS HEMOPNEUMOTHORAX.

Author.	Age.	Side.	Treatment* amount removed.	Result—Remarks.
Pitt ²⁹ (Case 2)	40	?	?	Fatal; tuberculous cavity.
Heise and Krause ¹³	21	L	400 cc.	Fatal; receiving art. pneumothorax.
Sardo ³¹	?	L	"Bloody fluid"	Recovery; was receiving bilat. pneumothorax for pulm. tuberc.
Leggett, <i>et al.</i> ²² (Case 2)	?	?	"Repeated"	Recovery. Receiving art. pneumothorax.
Sergeant ²²	31	L	1550 cc.	Recovery. Receiving art. pneumothorax for 3 years
Allan ² (Case 1)	20	L	Thor.	Recovery. Probable tuberculosis later.
Allan ² (Case 2)	38	R	Thor.	Recovery. Probable tuberculosis later.
Patino Mayer and Pataro ²³	32	R	?	Recovery. "Latent tuberculosis."
Holden ¹⁴ (Case 1)	32	L	1000 cc.	Recovery. Tuberculosis later (?).
Wilson ²⁷ (Case 2)	30	L	800 cc.	Recovery. Tuberculosis proven. Subsequent thoracoplasty.
Korol ²⁰ (Case 2)	38	L	?	Recovery. Tuberculosis later. Vesicle seen by Roentgen ray.
Pitt ²⁹ (Case 1)	18	R	Thor.	Fatal: bulla and torn adhesion found.
Rolleston ³⁰	21	R	Thor.	Fatal: bleeding point not found.
Boland ⁴	34	R	2170 cc.	Recovery.
Ness and Allan ²⁵	31	L	Thor.	Recovery.
Bushby ⁴	17	L	500 cc.	Recovery.
Williamson ²⁴	?	L	10,000 cc.	Recovery.
Fischer ¹¹	22	R	Thor.	Fatal. Diagnostic error led to laparotomy.
Kiaer ¹³	30	L	"Air and blood evacuated"	Fatal. No break found in pleura; no source of bleeding.
Bouchut and Beaupere ⁵	21	R		Recovery.
Doria ¹⁰	26	R	930 cc.	Recovery. Fluid replaced by nitrogen.
Hurxthal ¹⁶	29	R	3400 cc.	Recovery. Fluid replaced by air.
Terry ³⁴	34	L	950 cc.	Recovery. Oxygen tent for dyspnea; transfusion for bleeding.
Palmer and Taft ²⁷ (Case 1)	26	L	"Large amount"	Recovery.
Palmer and Taft ²⁷ (Case 2)	25	R	?	Recovery.
Milhorat ²⁴	21	L	2400 cc.	Recovery. Transfused for anemia.
Housden and Piggot ¹⁵	44	L	None	Fatal. Ruptured bleb and torn adhesion found.
Kjaergaard ¹⁹ (Case 1)	20	L	400 cc.	Recovery. Air injected on 5 occasions.
Kjaergaard ¹⁹ (Case 2)	25	L	"Few squirts of of blood"	Recovery.
Woll ²³	43	R	"Several times"	Recovery.
Leggett, <i>et al.</i> ²²	?	?	"A specimen of fluid"	Recovery.
Bellon ⁸	21	R	"Three times"	Recovery.
Staffier ¹²	24	R	Thor.	Recovery.
Frey ¹²	30	R	1220 cc.	Recovery.
Castex and Mazzei ⁷	35	R	?	Recovery.
Holden ¹⁴ (Case 2)	25	R	"Small amount"	Recovery.
Aguilar and Ferradas ¹ (Case 1)	37	L	200 cc.	Recovery.
Aguilar and Ferradas ¹ (Case 2)	29	L	200 cc.	Recovery.
Wilson ²⁷ (Case 1)	31	L	2745 cc.	Recovery.
Catuozzo ⁸ (Case 1)	27	R	200 cc.	Recovery.
Catuozzo ⁸ (Case 2)	27	R	500 cc.	Recovery.
Centeno, <i>et al.</i> ⁹	27	R	Thor.	Recovery.
Jones and Gilbert ¹⁷	23	R	2000 cc.	Fatal. Fluid replaced by air. Fibrin masses found at autopsy.
Korol ²⁰ (Case 1)	35	R	35 cc. plus air	Recovery. Developed empyema; tube drainage for 6 weeks.
Korol ²⁰ (Case 3)	?	L	3900 cc.	Recovery. Previous pleural effusion.
Korol ²⁰ (Case 4)	33	L	Aspirated 18 times	Recovery.
Hopkins (Case 1)	30	L	2000 cc.	Recovery.
Hopkins (Case 2)	30	L	120 cc.	Recovery. Only reported case in a woman.
Hopkins (Case 3)	30	L	200 cc.	Recovery

* Thor. = thoracentesis; amount removed not stated.

Case Reports. CASE 1.—A colored male, aged 30, was in good health until August 26, 1934, when he contracted an acute respiratory infection. While eating dinner on September 2, he choked on a piece of meat and coughed several times. After dinner he became aware of dull discomfort in the upper part of the left side of the chest. Within an hour the pain became more severe, and spread downward as far as the costal margin; it was definitely related to respiration. The pain grew worse and dyspnea increased; he was referred to this hospital the following evening. On admission there was obvious dyspnea, but no cyanosis was noted. The respiratory rate was 32 per minute and the pulse rate 132. The blood pressure was 114 systolic, 80 diastolic. Examination of the chest showed typical signs of a complete left-sided pneumothorax, with possibly a slight amount of effusion. The heart and mediastinum were shifted to the right. The right border of the area of cardiac dullness was found to be 12 cm. to the right of the midsternal line; the left border was apparently under the sternum. There was a soft systolic murmur heard over the body of the heart. The findings on physical examination were otherwise unimportant.

On the following morning, the patient showed extreme dyspnea. There were physical signs of an effusion extending upward as high as the angle of the scapula. A roentgenogram confirmed the presence of a complete pneumothorax with pleuritic fluid (Fig. 1). The blood pressure had fallen to 94 systolic, 70 diastolic. Thoracentesis was performed to relieve the respiratory distress. The intrathoracic pressure was +4 cm. of water. Air (1600 cc.) was removed; bloody fluid then appeared and 80 cc. of this was allowed to flow out before the needle was withdrawn. There was an astonishing improvement in the condition of the patient. His respiratory difficulty practically disappeared and during the day his blood pressure rose to 118 systolic, 82 diastolic. A blood count that day showed 4,300,000 erythrocytes; the hemoglobin was 90%. The pleural fluid had a hemoglobin content of 80%, indicating that it was largely blood.

The clinical condition of the patient remained good, but there was a gradual increase in the amount of pleural fluid. This eventually resulted in the return of dyspnea, and subsequent aspirations were performed to relieve him. During the next month, thoracentesis was performed on four occasions, with the removal of a total of 2800 cc. of fluid. The hemoglobin content of the fluid decreased progressively from 80% to a point where an accurate determination was impossible on the last specimen. If calculated on the basis of 100% hemoglobin, there was removed a total of 1250 cc. of blood in the 2800 cc. of fluid. During this time, the blood hemoglobin fell from 90 to 63%.

Repeated sputum studies were negative for tubercle bacilli. Guinea-pigs were inoculated with the fluid obtained by aspiration; they failed to show any signs of tuberculosis. The patient's lung gradually reexpanded. He was discharged 7 weeks after admission with no clinical or Roentgen evidence of pneumothorax, and only a very slight amount of pleural fluid, which subsequently disappeared entirely. He has been followed for 2 years without any evidence of pulmonary tuberculosis or other lung disease. He has gained weight, is working regularly, and has had no further symptoms referable to the lungs.

CASE 2.—A white woman, aged 30, had not felt well during the preceding year, but was never ill enough to lose time from her work—a clerical position. On August 20, 1935, she developed malaise, chilliness, fever, and some cough. She remained in bed for one day. On August 24, she felt a sudden sharp pain over the left side of the thorax; this persisted. She did not recall any previous strain or cough. She was admitted to the hospital 5 days after the onset of this pain.

The physical examination showed signs suggesting a partial pneumothorax on the left. A roentgenogram confirmed this and also showed the presence of a small amount of fluid. Although dyspnea was not trouble-

some, an exploratory thoracentesis was done. After 150 cc. of air had been removed, blood appeared; 120 cc. of this was removed. Unfortunately no cell count or hemoglobin determination was done on this fluid, but a smear showed that it contained a moderate number of intact erythrocytes and a large number of degenerating cells from which the hemoglobin had disappeared. No further aspirations were performed.

Under conservative treatment, the patient improved rapidly. Within 3 weeks the lung had completely reexpanded and the fluid had disappeared. Repeated sputum studies were negative for tubercle bacilli; guinea pig inoculations were also negative. Serial roentgenograms over a period of 11 months have failed to demonstrate any evidence of a tuberculous lesion in the lung. The patient is able to carry on her regular duties without discomfort.

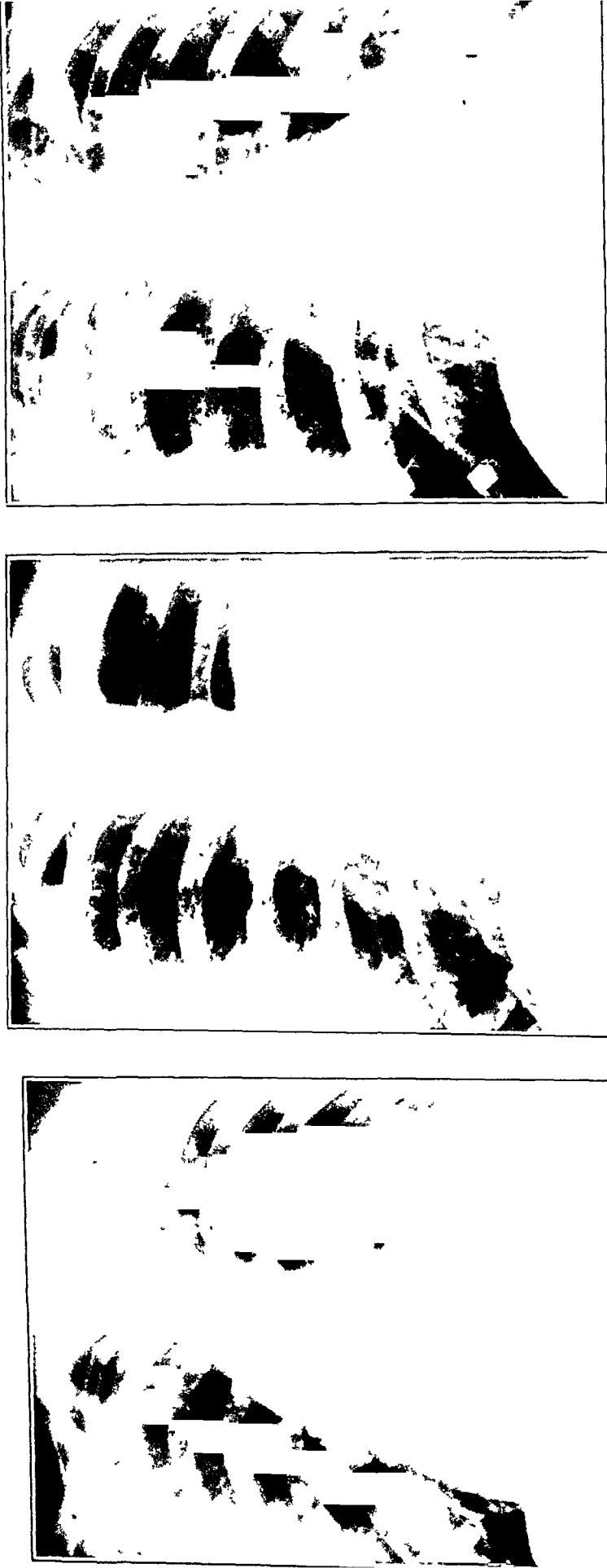
CASE 3.—A white male, aged 30, although never robust, had never been seriously ill. Several years ago, he had had an attack of sharp pain over the left side of the thorax; this had lasted only a few hours and had never recurred. He remembered no further details concerning it. On the afternoon of February 13, 1936, while shaving, he felt a sudden, severe, very sharp pain in the region of the base of the left lung. Within 15 minutes, the pain had spread upward to the shoulder and backward to the lumbar region. It was definitely aggravated by deep respiration. During the next half hour, the pain seemed to decrease somewhat and a short time later he reported for work at the restaurant where he was employed as night manager. The pain recurred and gradually became more severe. At 9 p.m. it suddenly became very severe and he collapsed but did not lose consciousness. He vomited once, and passed the night in a chair, because of dyspnea. The following morning a physician strapped the left side of the chest; this afforded some relief. However, the pain continued and gradually became most severe over the left lower quadrant of the abdomen. He was admitted to the hospital that evening, about 30 hours after the onset of symptoms.

Physical examination showed a dyspneic young man in obvious distress. The blood pressure was 108 systolic, 65 diastolic. The pulse rate was 108 per minute and the respiratory rate 30. There were typical physical signs of hydropneumothorax on the left side. The heart was apparently displaced somewhat to the right. A fluoroscopic examination confirmed the diagnosis. The films showed some irregularity at the apex of the partially collapsed left lung, suggesting a possible adhesion. On February 17, thoracentesis yielded air and 200 cc. of bloody fluid which did not clot. A cell count on this fluid showed 4,500,000 erythrocytes per c.mm.

The patient remained fairly comfortable. Physical examination and fluoroscopic studies showed that the amount of fluid was decreasing, so no further aspirations were attempted. On February 26, there was still a small pleural collection, but the pneumothorax had largely disappeared. Films showed that the right lung was clear. The upper portion of the left lung appeared normal; there were no gross lesions seen in the lower portion, but detail was somewhat obscured by the remaining fluid.

Repeated sputum studies were negative for tubercle bacilli. Smears and cultures of the pleural fluid were negative. Guinea pigs were inoculated; they failed to develop any signs of tuberculosis. During the past 6 months he has had no further symptoms referable to the lungs, and he appears to be in excellent health. The roentgenograms are normal (Fig. 2).

Historical Survey. Although Pitt²⁹ is usually given credit for calling attention to this condition in 1900, and for giving to it the present-day name of spontaneous hemopneumothorax, there are earlier reports of cases that were apparently of the same type.



A
B
C
 FIG. 1.—Case 1. (A) On admission. (B) After removal of 1600 cc. of air and 80 cc. of blood. (C) Appearance 7 weeks later.



.4
 FIG. 2.—Case 3. (A) On admission. (B) After removal of air and 200 cc. of fluid. (C) Appearance 5 weeks later.

Laennec²¹ described this condition, although he incorrectly attributed the presence of air in the pleural cavity to the fact that "the blood is sometimes decomposed and an aëriform fluid is disengaged, producing particular symptoms, as we shall see more particularly in the chapter on Pneumothorax." Later, he referred to an autopsy, in the course of which "upon penetrating the left side of the chest, a large quantity of inodorous gas made its escape with a hissing sound." The pleural cavity contained "about ten ounces of a bloody serosity." He also referred to the earlier report of Littré. From that time onward, there appear occasional reports giving fairly typical descriptions of this symptom complex, often under the misleading title of hemorrhagic pleurisy.

With the development of roentgenography, the definite demonstration of air and fluid in the pleural cavity became easier and more common. During the first two decades of this century, 7 definite cases of this condition were reported. During the past 15 years there has been an increasing amount of interest in this subject, and many additional reports have appeared (Table 1).

Aspiration for the relief of dyspnea in this condition was successfully used in this country by Whittaker³⁵ in 1876. He removed 34 ounces of bloody fluid and air from a chest, and was delighted to note the prompt improvement in the condition of the patient, who subsequently recovered without further complications.

Etiology. These cases can be divided into two groups. The first would include those which occur in persons who have tuberculosis; the second—a much larger group—those without demonstrable tuberculosis. In 2 of the fatal cases there had been rupture of a tuberculous lesion giving rise to an opening from the lung into the pleural cavity. In 6 of the patients who survived, subsequent examinations showed definite or suggestive evidence of tuberculosis. In these cases, one may postulate an etiology similar to that in the fatal cases. Three typical cases occurred in patients who were receiving therapeutic pneumothorax for known tuberculosis, presumably as a result of the tearing of adhesions containing lung tissue and blood-vessels, or from rupture of a caseous tuberculous focus.

In the majority of cases, tuberculosis could not be demonstrated. These represent merely spontaneous pneumothorax with bleeding as a complicating factor. The etiology of spontaneous pneumothorax is unsettled, but the evidence is accumulating to prove that in very many cases it is not due to tuberculosis. In his monograph on the subject, Kjaergaard¹⁹ reported follow-up studies on 49 cases. These patients were reëxamined at intervals ranging from 3 to 18 years after the initial pneumothorax. In only 1 case was there clinical or roentgenographic evidence of pulmonary tuberculosis. He also reviewed the cases reported in the literature. In 6 instances there had been found at autopsy superficial air vesicles at the pleural surface of lungs otherwise healthy. Microscopic examina-

tion showed that there was often a valve-like piece of tissue which would lead to a gradual increase in the pressure within the vesicle, and its eventual rupture. Roentgenologically, he was able to demonstrate such a vesicle on the surface of the lung in 1 patient, and a similar finding has been reported in hemopneumothorax by Castex and Mazzei,⁷ and by Korol.²⁰ Housden and Piggott¹⁵ found 2 subpleural blebs in their fatal case. This type of lesion could easily be missed unless roentgenograms were taken in various planes. Kjaergaard's conclusion was that spontaneous pneumothorax was usually a benign process, probably due to rupture of such vesicles, and rarely due to demonstrable tuberculosis.

If we accept this view, two possible sources of hemorrhage are apparent. A vessel in the wall of the ruptured vesicle may be torn, leading to a gradual accumulation of blood in the pleural cavity. In the autopsied cases, however, the walls of these vesicles have been very thin and have shown only small vessels. A more probable explanation is that the collapsing lung tears pleural adhesions containing blood-vessels; this has been proved in some of the autopsied cases. The occurrence of such adhesions is fairly common, as shown by Leopold and Lieberman.²³ They report that at autopsy adhesions were found in almost 50% of all persons above the age of 20, even after eliminating all cases with a history of acute or chronic pulmonary disease. In many cases these adhesions contain large blood-vessels. Rupture of adhesions with hemorrhage is one of the recognized complications of therapeutic pneumothorax, and the same thing undoubtedly occurs in spontaneous pneumothorax. The degree of elasticity of the adhesions determines the amount of collapse which may exist before such a rupture occurs. This explains the fact that in some patients the signs of hemorrhage appear early, while in others there is definite evidence to show that the bleeding does not begin until several hours after the initial pain and the appearance of signs of pneumothorax.

Symptomatology. This accident occurs most frequently in patients who have previously been in good health. The initial pain may occur while the individual is at rest, or it may appear on slight exertion. In many instances it is preceded by cough, sneezing, laughing, yawning, hiccup, straining or some other procedure that would suddenly alter the intrapleural pressure. The pain is usually localized at the onset, but later it may spread to involve one entire side of the chest, and in some instances it radiates to the abdomen also. Dyspnea may be slight or extreme. It appears after a variable length of time, depending upon the rate at which air enters the pleural cavity. When there is a valve-like opening, a high positive pressure with displacement of the mediastinum may develop. In many of the cases there has been noted a second sharp attack of pain occurring at any time from a few hours to several days after the original pain. Following this, signs of effusion

appear. The initial pain represents the onset of the pneumothorax; the second attack of sharp pain is due to the tearing of an adhesion. If the bleeding is slow, systemic signs of hemorrhage may not appear for hours or days, or may never appear. In several of the recorded cases the presence of blood has been discovered during a Roentgen examination or as an unexpected finding in the course of thoracentesis for the relief of dyspnea due to the accumulated air. In other patients the bleeding is more rapid and the signs of internal hemorrhage appear early in the course of the disease. In such cases, the physical signs of fluid in the pleural cavity are usually definite, and may even obscure the presence of air. In a few instances, the obvious signs of shock and internal hemorrhage, associated with pain which spreads to the upper abdomen, have led to a tentative diagnosis of an acute surgical lesion of the abdomen. Fortunately the correct diagnosis has usually been made before subjecting these patients to a laparotomy, but in one instance¹¹ the error was not discovered until after operation.

Treatment. No uniform treatment can be outlined; each case requires individual consideration. Control of the bleeding and treatment of shock are the emergencies which must first be met. These demand absolute rest, with the liberal use of sedatives if necessary. Roentgen examinations should be postponed for several days, unless portable equipment is available. Relief of dyspnea comes next. An oxygen tent may suffice.³⁴ If dyspnea is severe and persistent, it may be necessary to allow the escape of some air or fluid; this can be done most safely with a pneumothorax apparatus. No attempt should be made to continue the aspiration to the point of producing a negative pressure. The value of pneumothorax in controlling pulmonary hemorrhage in tuberculosis is well known, and a high intrapleural pressure with a collapsed lung should promote hemostasis in these cases also. A large transfusion or the intravenous injection of fluid carries with it the danger of raising the blood pressure and prolonging the bleeding. Small transfusions are justifiable in an effort to promote clotting, or if the anemia becomes extreme. Blood aspirated from the pleural cavity has been injected into the patient's vein,¹⁷ but this procedure is not recommended as a routine measure. The intramuscular injection of whole blood is a harmless procedure, and although it has not been tried in these cases, there is evidence to show that it has a definite hemostatic action. Several authors have suggested that if bleeding persists, a thoracoscopy or thoracotomy might be performed in an attempt to locate and treat directly the bleeding point. Such a procedure would be of doubtful value; in 2 of the fatal cases,^{18,30} the authors have been unable to locate the site of bleeding even at the autopsy table.

If the patient survives the first critical stage and the bleeding ceases, the question arises as to whether or not the blood should be

aspirated. A survey of the literature shows that the patients who were not subjected to repeated aspirations seem to have done as well as those who were tapped repeatedly. It has long been known that blood in the pleural cavity shows little tendency to clot. Pagenstecher²⁶ showed that blood which had remained in the pleural cavity for 6 hours had lost its power to clot; this observation has been confirmed repeatedly. He believed that the pleura exerted some protective action, and compared it to the vascular endothelium in its ability to maintain blood in a fluid state. Recently it has been claimed that respiration acts mechanically to defibrinate the blood, and that the fibrin is deposited on the diaphragm and pleura. Jones and Gilbert¹⁷ attribute the fatal outcome in their case to the formation of fibrin masses which eventually caused circulatory failure. In other cases which have come to autopsy such massive deposits of fibrin have not been recorded. If repeated aspirations are carried out, they should not be done with the hope of preventing this complication; Pagenstecher's work would indicate that if defibrination occurs, it takes place rapidly and is complete before one could be certain that active bleeding had ceased.

Blood in the pleural cavity is slowly absorbed. If the amount is small, it is justifiable to delay thoracentesis for at least a week or two. If there is evidence that the amount of fluid is decreasing, nothing need be done. If it has not decreased appreciably, it should be withdrawn. If fluid is present in large amounts it may give rise mechanically to pressure symptoms which are sufficient to justify its early removal. In several instances,^{37,19,17,10,16} air or nitrogen has been injected into the pleural cavity as the blood was removed, to maintain compression of the lung and to minimize any tendency toward recurrence of the bleeding. This should always be done when any considerable amount of fluid is removed. It has been claimed that calcification of the pleura may result if the blood is not completely aspirated; this complication has not been reported in any of the cases reviewed, but as it is a process which may require years to develop, it may be reported later.

The patient should remain under observation for months after his apparent recovery. Although recurrent spontaneous pneumothorax is well known, there are no recorded cases of recurrence of hemopneumothorax. It is probable that the fibrin deposits, or the presence of blood in the pleural cavity with a resulting sterile pleurisy, leads eventually to the formation of such extensive pleural adhesions that subsequent collapse and bleeding become impossible.

Age, Sex and Side Involved. An examination of Table 1 shows that this is predominantly a disease of early adult life. Of 44 cases in which the age is stated, 26 occurred between the ages of 20 and 30, and 16 between the ages of 31 and 40. This corresponds with the usual age of most strenuous physical exertion, but exercise does not seem to be immediately concerned with the onset of symptoms.

The overwhelming proportion of cases in males is difficult to explain. If these abnormal air vesicles are the result of developmental defects, one would expect to find them in females as frequently as in males. If latent tuberculosis plays any part, one might expect a higher incidence in women. If physical exertion is of importance in the development of the predisposing factors, one would expect that with the entrance of girls and women into strenuous types of sport and work there would appear an increasing number of cases in this sex. No known explanation on an endocrine basis has been advanced.

The side involved is apparently a matter of chance; each side has been involved in approximately the same number of cases.

Summary and Conclusions. Three cases of spontaneous hemopneumothorax are described, including the first recorded instance of this condition in a woman. Forty-six cases reported since 1900 are briefly summarized.

A majority of the cases have occurred in persons who had no demonstrable pulmonary tuberculosis or other disease of the lungs. The etiology of this condition is not proved, but it is probably due to the rupture of an emphysematous subpleural air vesicle, followed by the tearing of preëxisting pleural adhesions which contain blood-vessels.

During the first 48 hours, aspiration is justifiable for the control of dyspnea but not as a routine measure. When the bleeding has stopped, the fluid should be removed and replaced by air.

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OIL OF WINTERGREEN (METHYL SALICYLATE) POISONING.

REPORT OF THREE CASES, ONE WITH AUTOPSY, AND A REVIEW OF THE LITERATURE.

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As is shown by the literature, poisoning by oil of wintergreen is of rare occurrence, but its apparently increasing frequency and the circumstances under which it occurs make it of especial interest. The subject was brought to the author's attention by a case upon which he recently performed an autopsy. The purpose of this paper is to report 3 new cases, including 1 fatal case with autopsy,* and to reiterate the fact that oil of wintergreen is a deadly poison and should officially be publicized as such. The reports of 43 cases were culled from the literature, of which 13 included necropsy findings.

The mortality of the whole series was 59%; 41% occurred in infants, all of whom drank oil of wintergreen from a bottle left within their reach by unsuspecting parents, who were astounded to find out that the substance which they used as a liniment was a potent poison. In 2 instances the liniment was drunk by inebriated adult chronic alcoholics evidently craving something stronger than whiskey.^{49, 63} In France and Germany, the bottles are usually marked either "For external use only" or "Poison," and 4^{4, 11, 34, 62} of the 5 cases found in the French literature were deliberate suicides. One woman⁵¹ took the substance hoping to produce abortion. It has been reported that native African women in some isolated tribes in Northern Rhodesia commit suicide by filling their vaginas with powdered bark from the root of a native species of milkwort, and an analysis of this bark has shown it to contain a considerable quantity of methyl salicylate.⁶² In the remaining 86% of this series, the poisoning was accidental.

The earliest cases on record are to be found in the 1832 edition of T. R. Beck's "Elements of Medical Jurisprudence," and are likewise repeated in the later edition;⁶ 55% of the cases have occurred during the past 16 years and are spread out rather evenly over this period (Table 1).

* From the Harriet Lane Home of the Johns Hopkins Hospital.

Of the 4 cases in the files of the Harriet Lane Home, 1 has been reported.⁵⁰ The others are presented briefly below, all inconsiderable negative findings being omitted.

Case Histories. CASE 1.—W. B., (H.L.H. 54742), male, white, aged 2 years. *Past history:* non-contributory. *Present illness:* One morning, September 23, 1927, the infant drank about 15 cc. of oil of wintergreen. He vomited one-half hour later, and the vomitus smelled strongly of the drug. He continued to vomit all day, asked for water and vomited it. However he did not vomit for 6 hours during that night. Six hours after taking the poison he began to breathe deeply and this symptom increased during the night and the next morning, when he was also found to be deeply cyanotic and his urine showed 4+ acetone and salicylate tests. Because of the hyperpnea and cyanosis, his father, a doctor, brought him to the hospital.

Physical examination: (3 P.M., September 24, 1927, 29 hours after taking the poison). Temperature 104° F., pulse 180, respirations 60, blood pressure 105/60. The child was well developed and nourished and was prostrated. He lay limply in the arms of his mother and responded only slightly. His skin was generally cyanotic, with a marked pallor about the nose and mouth; the corners of the mouth twitched occasionally. The respirations were rapid and deep, of typical air-hunger type. The pulse was weak and rapid, but regular. The eyes showed contracted pupils, injection of the conjunctivæ, and a tendency for them to roll upward under half-closed lids. The mouth was dry and the buccal mucous membranes were not injected. The breath was acidotic. The heart sounds were of poor quality. The abdomen was moderately distended but not tender. The tendon reflexes of the arms and legs were hyperactive.

Urinalysis: Specific gravity 1.022, acid reaction, sugar 0, albumin trace, acetone 5+, diacetic acid and salicylate (FeCl₃ test) 5+. *Microscopic examination:* occasional red blood cells. *Blood chemistry:* CO₂ combining power 24.9 vols. %.

Treatment and Course: On admission the child was given caffeine and adrenalin, and the stomach was lavaged with 6% sodium bicarbonate, 2 gm. of the salt being put through the tube and left in the stomach; 100 cc. of 5% glucose was given intravenously, followed by a transfusion of 300 cc. of whole citrated blood. The color and pulse improved but hyperpnea persisted and the cheeks became flushed. By night on the day of admission the respirations had slowed up slightly but still remained deep. The child drank 5% glucose thirstily, and was given 1.2 gm. of sodium bicarbonate every 3 hours. Later on, there was evidence of excess mucus in the throat and 0.13 mg. of atropine was given with beneficial effect. Late the first night in the hospital the child refused to drink fluids. To counteract this, 75 cc. of a mixture of equal parts 5% sodium bicarbonate and 5% glucose was given per rectum every 3 hours, preceded each time by a soft soap enema. Early the next morning he received 300 cc. 5% glucose intrasynously, preceded by 3 mg. morphine. By morning (September 25, 1927), the child was brighter and responded to his name; pulse 160 and better quality, temperature 102.8° F., respirations 48 and deep, cyanosis marked. At noon he was given a 250 cc. blood transfusion with 100 cc. normal saline. After this his blood pressure was 95/60. That night there were signs of pneumonia at both bases and his pulse was 180 and weak. Digifoline was given, 1 ampule every 3 hours for 5 doses. The next morning, 72 hours after taking the poison, the child was greatly improved; pulse 120 and good quality, cyanosis less, and respirations less deep and rapid. The temperature was 100.6°, and the lung signs were less marked. The infant asked for food.

TABLE 1.—METHYL SALICYLATE POISONING.

Author.	Date.	Sex.	Age.	Dose in cc.	Symptoms and signs.												Blood studies.					Urinalysis.			Outcome.		Treatment and remarks.	
					Minutes elapsed before symptoms appeared.	Vomiting.	Abdominal pain (burning).	Rapid respirations.	Deep (Kussmaul) respirations.	Rapid pulse.	Marked cyanosis (terminal or early).	Flushed skin.	Extreme thirst.	Stupor and coma.	Convulsions.	Impaired hearing or tinnitus.	Dimness of vision.	Temperature when first seen.	Leucocytes (thousands per cumm.)	Hemoglobin in %.	CO ₂ combining power (in vol. %).	Non-protein nitrogen.	Sugar.	Salicylate.	Acetone.	Albumin.		Recovered.
Pyle	?	M	0	?	..	+																			Yes	?	6 soldiers drank "tea" with m. salic. flavoring.	
Pyle	1832	M	7	30		+																			No		No treatment.	
Gallagher	1852	M	9 yrs.	10		+																			Yes		(Colonel, Philadelphia. Delirious, very hungry.	
Jewett	1867	F	35 yrs.	15		+																			No	?	No treatment. Early failure of sight and hearing.	
Hamilton	1875	F	Adult	16		+																			Yes		No treatment. Developed left hemiparesis.	
One reported by S. V. Allen	1885	M	30 yrs.	250	30		+																		No	17	Alkali; purgatives which did not act.	
Hallermann	1886	F	29 mos.	12	71		+																		No	18.5	Seen by doctor 20 min. before death.	
Parkham	1887	F	25 yrs.	30			+																		No	15	No treatment. Took m. salic. to produce abortion.	
Spill	1900	M	9 yrs.	15	360		+																		Yes		No treatment.	
Van Wageningen	1900	M	2 yrs.	3		+	+																		No	48	Emetics, cathartics, eggs and milk 7 hrs. after poisoning.	
Pillbury	1900	M	Adult	60	120		+																		No	25	Persistent diarrhea and sweating.	
Prior and English	1903	F	2 yrs.	4	120		+															+			No	10	Emetics ineffectual. Respiratory failure and death.	
McNetherly	1903	M	3 yrs.	12	150		+																		No	7	No treatment.	
Reynolds	1903	M	28 yrs.	12			+																		Yes		No treatment.	
Moyn and Brecht	1914	M	3 yrs.	12		+																			Yes	?	Recovery in 7 days. Glucose and alk. proctoclysis.	
Reese, Evans and Johnson	1918	M	40 yrs.	30	20		+																		Yes		Both drank oil of wintergreen with ginger ale at a dance; 1 died later "that night," the other recovered.	
Meyer	1920	M	2 yrs.	30	60		+																		Yes			
Howard	1921	M	21 yrs.	6		+																			Yes			
Howard	1921	M	21 yrs.	6		+																			No	?		

Blood studies: hemoglobin 85%, white blood cell count 8000. No methemoglobin.

Urinalysis: albumin +, acetone 2+. Microscopic examination: a few red blood cells and hyaline casts.

The following day, September 27, 1927, the child was playful and well, but very weak. The respiratory rate was 38, the lungs were clear, and the urine showed only a faint trace of acetone and salicylate; the remaining convalescence was uneventful.

CASE 2.—J. M. (H.L.H. 67018), female, white, aged 22 months. *Past history*: non-contributory. *Present illness*: At noon, on May 10, 1930, the baby drank "one mouthful" of oil of wintergreen but immediately vomited it. She vomited everything she ate thereafter. Six hours following the poisoning, she began to breathe deeply, but did not complain of pain and was drowsy.

Physical examination: (3 A.M., May 11, 1930, 14 hours after ingestion of the poison). Temperature 100°. The child was well developed and apparently overnourished. The pulse was of good quality, and the respirations were rapid, deep, full and strong, being of typical air-hunger type. There was no cyanosis and the skin was of good color. The child lay stuporous until aroused and then resisted examination. The pupils were equal and reacted normally. The throat was markedly injected. The lungs were clear and the heart sounds normal. There was no abdominal distention. The deep reflexes were normally active.

Urinalysis: amber, 1.012, acid reaction, albumin 0, sugar 0, acetone 3+, diacetic acid and salicylate 3+. Microscopic examination: a few granular casts. Blood studies: Hemoglobin 65%, white blood cell count 10,000 (neutrophils 48%, lymphocytes 52%).

Treatment and Course. On admission she was given 250 cc. of equal parts 10% glucose and normal saline intravenously. About 8 hours later the hyperpnea was still marked and the child was sleeping deeply. She was then given 100 cc. 5% sodium bicarbonate and 100 cc. 5% glucose intravenously. This was repeated 6 hours later, and the child seemed greatly improved. At night, 33 hours after taking the poison, the child was practically well and the hyperpnea had all but disappeared. The next day she was well and the urine was negative except for a positive acetone test. On May 13, 1930 the urine was negative, and the following day the patient was discharged.

CASE 3.—A. C. (H.L.H. 59309), female, colored, aged 1 month, at 5 P.M., on November 4, 1935, was given 5 cc. of oil of wintergreen by an imbecilic child. Half an hour later the baby cried, choked and looked flushed, so the mother nursed her. The infant immediately vomited a white milky fluid which smelled strongly of wintergreen. Following this she seemed sleepy and refused breast and water. The mother noticed that the infant was "short of breath," but seemed very sleepy and did not cry. Two hours later the infant vomited again, the vomitus still smelling of wintergreen. At 9 P.M. a local doctor was called and he prescribed 5 cc. peppermint water every 3 hours. Soon after this, the mother gave 5 cc. castor oil and at midnight the infant had a copious stool, which also smelled strongly of wintergreen. She became more drowsy and hyperpneic through the night, and the next morning she "wouldn't wake up" and seemed "painful whenever touched." She had several more stools and voided a few times, and finally was brought to the hospital.

Physical examination. (1.30 P.M., November 5, 1935, 20½ hours after the poisoning). Temperature 105.6° F. The infant was comatose and occasionally lifted her legs up and cried feebly as though she had abdominal pain. Her respirations were very rapid and deep, of typical Kussmaul type. Her breath was acidotic. She was pale but not definitely cyanotic. The pupils

reacted to light and showed an intermittent, rapid, horizontal nystagmus. The lungs were clear, the pulse very rapid but of regular rhythm; the heart sounds were clear. The abdomen was soft and no masses were felt.

Blood studies: Wassermann reaction negative, blood culture sterile, CO_2 combining power 41 vols. %, total fixed base 167.6 cc./N/10.

Treatment and Course. The infant was given oxygen by mask immediately on her arrival at the hospital. Caffeine was given while preparations were made to administer intravenous fluids and a blood transfusion, but the baby died just as the fluids were begun, $23\frac{1}{2}$ hours after taking the poison.

Autopsy (No. 14495, 18 hours after death). The body weighed 4 kilos. and measured 54 cm. in length. The nutrition was average. The only lesions found macroscopically were a number of subpleural and subepicardial hemorrhages, some of which measured 8 by 4 mm. In the myocardium of the posterior wall of the left ventricle one small hemorrhage was found. There were small patches of edema in the lungs. The bladder was distended with 200 cc. of cloudy urine.

Microscopically, the sections showed little. In the lungs there were some areas of edema and hemorrhage but no distinct pneumonia. Some of the bronchioles in places had lost their epithelium and their walls contained neutrophils and eosinophils. A coagulum containing leukocytes and red blood cells was present in the lumen; a bacterial stain showed an occasional Gram-positive diplococcus, and these were not lancet-shaped. The sinusoids of some of the bronchial lymph nodes were engorged with old blood cells. No lesions were found in sections of the optic nerves, brain, spinal cord, kidneys, liver, spleen, pancreas, thymus, adrenals, heart, aorta, esophagus, stomach, intestines, costochondral junction of the rib, bladder, and mesenteric lymph nodes.

Anatomical Diagnosis. History of accidental methyl salicylate (oil of wintergreen) poisoning. Petechial hemorrhages in pleuræ and epicardium. Slight edema and hemorrhage of the lungs. Acute bronchitis (aspiration).

The 3 above cases and the case reported by Pincus and Handley⁵⁰ (Table 1) show a uniformity of symptoms and signs and present a definite clinical picture of this type of poisoning. All 4 of the infants vomited some oil of wintergreen shortly after taking it and vomited frequently thereafter. The deep and rapid respirations, found in each of these cases, came on after about 6 hours. The odor of oil of wintergreen was present in the stools and in the urine of 1 case.⁵⁰ Early cyanosis was found in the first of the new cases but in none of the other 3, while marked terminal cyanosis was seen in 1 of the 2 fatal cases. Two showed flushed cheeks while the other 2 were generally pale. An injected pharynx was seen in 1 case, while another showed bright red lips. All of the infants had sweetish breath (acetone?) and their blood CO_2 combining powers varied between 24.9 and 41 vol. % on admission. In 2 of these cases the conjunctival and scleral vessels were congested and the conjunctivæ injected; in 1 case the pupils were contracted, but in all they reacted to light. In each infant, the lungs were clear on admission, and while the pulse was fast, it was regular and usually of fair quality. In 1 case the abdomen was distended but in none was it tender. In 2 instances the tendon reflexes were hyperactive, while in 1, in which the baby had probably got very little poison and retained

only a fraction of this, they were normal. The infant seen after 20 hours was comatose; she had swallowed 5 cc. of the poison and was 1 month old. The one seen after 29 hours was semistuporous; she was 2 years old and had swallowed 15 cc. Another, seen after 14 hours, was "stuporous until aroused and then resisted examination;" she was 2 years old and had swallowed "about one mouthful" of the poison. Pincus and Handley's 2-year-old child "was able to sit and stand alone, though his actions were slow and deliberate," and he was seen at 10 hours and had taken an amount "not exceeding 60 cc." In all cases the temperature on admission was variable as was likewise the white blood cell count. The one infant which had a blood non-protein nitrogen determination showed it to be 62 mg./100 cc. Urine specimens were obtained on only 2 of these cases (both of whom recovered), and casts were found in both, while 1 of them (H.L.H 54742) showed a trace of albumin.

Pincus and Handley's case finally had convulsions and twitchings of muscles of the hands and face, while one of the above showed twitchings of the corners of the mouth. One infant showed a great thirst at times, which has been recorded as a frequent symptom. None have shown surgical shock, but in one the extremities were cold 8 hours after taking the poison and 6 hours before death.⁵⁰ Respiratory failure marked the terminus of the 2 fatal cases.

The case reported by Price and L'Engle⁵² is of especial clinical interest in that they saw the child continuously from 1 hour after it had taken the poison until its death 9 hours later, and they do not report that it received any treatment other than gavage. They found that the child, a 2-year-old girl, had swallowed 4 cc. of commercial oil of wintergreen, and had vomited several times before coming to the hospital. On arrival at 9.30 A.M., she was still vomiting, but this ceased following the gavage. Examination showed a temperature of 98.6° F., pulse 100, regular and of good volume; respirations were 26 and regular.

The following quotation will best describe the clinical course:

"There was nothing abnormal in the child's appearance, and it showed no evidence of suffering pain. There were no further symptoms for 2 hours, when the patient seemed to have pain in the abdomen, was drowsy, and complained of great thirst. The pulse rate increased to 150 and within an hour the child's face became flushed, the respirations were somewhat labored and irregular, and there were evidences of impaired hearing and some hallucinations of vision. The temperature was not increased but there were slight twitchings of the hands and the muscles of the neck, and at this time delirium was first noticed. There was diarrhea and a strong odor of oil of *Gaultheria* in the stools.

"At 3 P.M. the temperature was 99.4, pulse 132 and of good volume, respirations regular but somewhat labored. At 3.30 P.M., 7 hours after the drug had been taken, the child had a general convulsion, in which the arms and legs were extended, eyes rotated upward, head thrown back, neck rigid, but there was no arching of the back. The pupils were equal and were moderately dilated. This tonic spasm lasted about half a minute and

recurred at frequent intervals. The pulse was of fair volume but was slightly irregular, and the respirations were deep, labored, and gradually decreased in rate to 4 or 5 per minute. These symptoms increased until, finally, the child died of respiratory failure at 6.30 P.M., 10 hours after ingestion of the poison."

In Table 1 we find that the smallest lethal dose of the poison was 4 cc., and this occurred in 2 instances: One was in a 17-month-old infant who vomited it immediately,²⁹ and the other was a 2-year-old infant who had a persistent diarrhea.⁵² The former was given emetics effectually but no other treatment, and died after 12 hours; the latter died in 10 hours, no treatment being given. The author's case (H.L.H. 59309), an infant of 1 month, swallowed about 5 cc. of the drug and vomited it a half hour later. It had no early treatment and died after 23 hours, shortly following its arrival at the hospital. Six cc., the smallest lethal dose in an adult, was taken in 2 instances,²⁸ in 1 of which the victim died after a few hours. Thirty cc. was lethal in 2 instances,^{2,51} and they died 15 and 34 hours, respectively, after taking the poison. The former received no treatment. The latter received alkali fluids by mouth, a diuretic, and cardiac stimulants 10 hours after the poisoning; subcutaneous and intravenous lactate solution and subcutaneous oxygen were administered after 26 hours, when the patient had a sudden sinking spell.

The most rapid death occurred in 10 hours.⁵² This was in an infant who took 4 cc. of the poison and who evidently received no treatment. Hughes' case²⁹ died in 12 hours and received emetics immediately after taking the poison. The most rapid death in an adult⁵¹ was in 15 hours; she took 30 cc. and received no treatment. The average time before death in the infants was 21.3 hours, while in the adults it was 23.4 hours.

The most common symptom was vomiting, and it occurred in 87% of the cases; 33% had abdominal pain or burning. Rapid respirations and pulse were the most common signs, each occurring in 59% of the cases. In only 43% were deep respirations reported, and 35% of these recovered; 49% showed stupor and coma, of which 26% recovered; 40% had convulsions, with only 17% recovering, thus making convulsions the gravest prognostic sign. Flushed skin was found in 35% of the cases, and thirst in 26%. Cyanosis was found in only 22%. Tinnitus and dimness of vision occurred in 17% and 15% of the cases respectively. The temperatures given in the table are those taken when the patient was first seen by a doctor, which varied between 1 and 26 hours after the ingestion of the poison; it has been found that the temperature remains at 98.6° for about the first 6 hours. The blood counts were variable and apparently of no special prognostic value.

The lowest CO₂ combining power of the blood was 24 vol. %, and it was found in the infant reported by Pincoffs and Chambers.⁴⁹

Despite treatment it died in 23 hours with terminal respiratory failure. The next lowest value for this blood property was 24.9 vol. %. It was found in one of the author's cases (H.L.H.54742), and, as was related above, this child recovered in about 80 hours. The average CO₂ combining power was 32.7 vol. %. Only two blood non-protein nitrogen determinations were found,^{49,50} and these were 62 and 79 mg./100 cc. (of whole blood). The former was in an infant who died in 14 hours, and the latter in an adult who apparently recovered from the poison after 48 hours to develop pneumonia 2 days later and die of it in another week. The blood sugar readings have varied between 130 and 170 mg./100 cc. One case⁵⁷ is reported in which glycosuria was discovered and the blood sugar proved to be 148. Of the 5 instances in which it was reported, the average blood sugar was 152, and all but 1 of these patients recovered. Of the 15 reported tests for salicylates in the urine all were positive; 11 of the 12 tests for acetoneuria were positive, while 7 out of the 12 cases tested showed albuminuria. Two of the cases, Meyerhoff's⁴¹ and the author's (H.L.H. 59309) showed anuria. The bladder of the former, at autopsy, was practically empty, while that of the latter contained 200 cc. of urine.

The reports of 13 autopsies on cases of oil of wintergreen poisoning were found in the literature, and despite the fact that the terminology in some was indefinite and that the lesions described may well have been due to postmortem change, they, with the author's case, are briefly summarized in the following paragraph.

These patients died between 12 and 36 hours after taking the poison. Nearly half of the autopsies showed "generally engorged blood vessels," subepicardial hemorrhages, "congestion" of the gastro-intestinal tract, edema of the lungs, engorgement of the small vessels of the lungs, engorgement of the small vessels of the kidneys, and "cloudy swelling" of the renal tubule cells. The following conditions occurred in 30% of the cases; visceral subpleural hemorrhages, hemorrhages into the lung parenchyma and alveoli, "fatty degeneration" of liver cells, and lymphoid hyperplasia of the spleen. "Congestion" of the glomeruli, "fatty degeneration" of the tubules, and necrosis of the tubule cells were renal conditions found in 22% of the autopsies. Hyperplasia of the lymphoid tissue of the gastro-intestinal tract was reported in 3 cases,^{3,41,63} but this condition was not found in the author's case.

None of the reports described the peculiar patchy marked inflammation and epithelial destruction of a few of the bronchioles found in the author's case. Since the infant was reported to be well before taking the drug and only a very few bacteria were found in the affected bronchi in the bacterial stains, it seems likely that the peculiar bronchitis may have been the result of aspiration of the drug.

Thus, there are no specific anatomic pathologic changes in these cases, and those which are found are fairly inconstant and do not present a picture which is typical in any way. Of greater importance are the physiologic pathologic changes, which will be reviewed in the summary of the pharmacologic investigations of the salicylates which follows.

In 1885, it was found¹ that the drug acts centrally in abolishing voluntary and reflex action and peripheral sensitivity; that with small doses of the drug the pulse is accelerated, the respiratory rate is increased, and the blood pressure is first depressed slightly and then increased, while, with large doses a permanent depression of all three occurs; that the ultimate fall of blood pressure is due to the poisoning effect of the drug on the heart and the peripheral vessels. The next year experimental evidence showed⁶⁴ that the drug has a direct effect upon the respiratory and cardiac "centers" in the medulla, and a recent article,³² among other things, clearly bears out this fact.

The drug,^{14,40} unless given in amounts much greater than the therapeutic dose, has no toxic effect upon the myocardium. Hoke²⁷ refers to the salicylates as being in the same class as histamine with regard to their property of paralyzing the smooth muscle of the small vessels, causing a marked dilatation of them. Methyl salicylate, given intravenously, apparently injures the capillary walls, especially in the lungs, where this injury results in the pulmonary edema frequently evidenced clinically and found anatomically at autopsy.^{9,58,60}

The analgesic effect of small doses of acetyl salicylic acid is common knowledge and practice among laymen. The general toxic effects of sodium salicylate, acetyl salicylic acid, and methyl salicylate are the same and are due to the salicyl radical. The average oral dose of methyl salicylate U.S.P., is 0.75 cc. and 2 cc. is listed as the maximum dose. As has been stated, 4 cc. has been lethal in an infant, and 6 cc. in 2 adults. The toxic symptoms of dizziness, tinnitus, nausea, and vomiting are usually brought on by 2 to 3 cc. of the drug by mouth. The average toxic dose of methyl salicylate is two-thirds that of salicyl-salicylic acid and one-half that of sodium salicylate.³⁶ Commercial natural oil of wintergreen, of specific gravity 1.17, is 97% methyl salicylate and 3% terpene; commercial natural oil of birch is all methyl salicylate.¹ There is no difference in the toxicity and potency of the natural and synthetic forms of methyl salicylate.⁵⁸ Clinically, sodium salicylate and methyl salicylate poisonings are essentially similar.

Free salicylic acid in the stomach leads to nausea, burning, diarrhea and vomiting,⁴⁴ and these are believed by some to be due to the local irritation. In methyl salicylate poisoning, the epigastric burning is more intense than that of other salicylates.²⁹ It is also

thought by several writers ^{13,22a} that the salicylates have a central emetic action.

Small to moderate doses of sodium salicylate in animals and humans cause a slight diuresis;⁷ full toxic doses a diminution of diuresis. This latter has been ascribed to both diaphoresis and diminished renal functional efficiency.^{24,55} Further investigation,^{21,25} showed that toxic doses of the salicylates in both normal and sick patients may cause not only some degree of anuria, retention of blood urea and non-protein nitrogen, a decrease in phenolsulphone-phthalein excretion, and albuminuria, but also the appearance of white blood cells and hyaline casts in the urine. Eight cases gave clinical evidence of impaired renal function (albuminuria or increased blood non-protein nitrogen) (Table 1), and the thorough blood studies in the case of Pincus and Handley⁶⁰ show a retention of phosphate, a marked chloride retention, a decrease in total base, a marked increase in non-protein nitrogen, and an albumin-globulin ratio of 1 : 1. Unfortunately, permission for autopsy on this case could not be obtained; in the case which the author autopsied, no blood non-protein nitrogen or urea determinations were made and no urine obtained for study. However, in the autopsies thus far reported, there have been no definite anatomic pathologic lesions that correspond with the clinical evidences of renal functional impairment.

The antipyretic and diaphoretic property of the salicylates has been recognized and studied,^{16,24} and was especially noticed clinically in some of the earlier cases of poisoning.^{21,48,61} Only a very small amount (0.1 % of dosage given) of salicyl is excreted in the sweat.^{56b} The diaphoretic and vasodilatory action of these drugs are thought to be connected.

The esters of salicylic acid are absorbed by the skin more readily than the acid or its salt,²⁹ and the salicyl radicle has been detected in the urine 30 minutes after the skin application of oil of wintergreen.³⁵ Only the soluble sodium salicylate salts are absorbed in the stomach, and apparently no hydrolysis of methyl salicylate takes place there.⁸ Very little hydrolysis of methyl salicylate takes place in the gastro-intestinal tract,²³ and at autopsy, in 3 instances,^{4,22,41} the "odor of the drug" has been noticed in the intestines, and, clinically, in the urine and stools in 2 cases (I.L.H. 59309).²² Thus, it seems probable that methyl salicylate is absorbed as such from the intestine. The salicyl radicle has been recovered from every body fluid and organ²⁹ following ingestion of methyl salicylate, but free salicylic acid has never been demonstrated in body fluids,^{56a} and this is due to the fact that the average pH of the blood would not permit it.

Heat production is increased in salicylate poisoning, but, it is believed, through the dilated vessels and diaphoresis this heat is lost.²² Nitrogenous metabolism is generally increased, and, in

patients given toxic doses of salicylate, the total nitrogen in the urine may show a 40% increase.¹⁰ This is mainly due to increased uric acid excretion,⁷ which is thought to be due to decreased uric acid catabolism in the blood.^{18,53} The salicylates cause an increase in the blood lactic acid,^{23,32} and in general also in blood amino-acids. Urinary ammonia is diminished,⁴⁵ and this fact points either to decreased deaminization or to impairment of renal function.

Glycosuria has been found in methyl salicylate poisoning.⁵⁷ Hyperglycemia, as can be seen in Table 1, occurred in all 5 cases where this determination was made.^{46,49,50,57} Of the 12 cases examined for acetonuria, only 1 was negative, and of the rest, many gave a 4+ reaction.

Ingested sodium salicylate is recoverable from the urine to the extent of 80% in the form of a salicylate, and its excretion takes place over a period of 3 days.²⁰ On the other hand, ingested methyl salicylate is only 51% recoverable from the urine as the salicyl radicle, and its excretion is completed in 4 days. Of the methyl salicylate, 0.1% has been recovered still in its original form. To this relative retention of methyl salicylate is attributed its greater toxicity.²⁰

The similarities of the symptoms of diabetic acidosis and salicylate poisoning have long been recognized, and Table 1 shows a markedly decreased blood alkali reserve (CO_2 combining power) in the 9 instances where this value has been reported. Despite evidence to the contrary,^{43,56a} it is generally found that a decreased alkali reserve ("acidosis") does occur when toxic doses of the salicylates are given to animals and humans, and that it is not due to the products of fat metabolism alone, as in diabetes,⁴⁵ but also to the liberation or accumulation of other fixed acids in the blood.³² There is thus usually a compensated fixed acid "acidosis."

In 6 of the cases listed no vomiting was reported (Table 1); of the 4 Harriet Lane Home cases, 1 infant (H.L.H. 59309) vomited only twice, the others vomited more or less continuously for the first few hours. With regard to the effect upon the blood acid-base equilibrium of protracted vomiting, it is found that there is some divergence of opinion. Theoretically, a loss of HCl, due to vomiting, would produce an alkalosis. Actually, in children, vomiting is more often associated with an "acidosis"⁴⁷ in which, in severe cases, the intense air hunger, rapid pulse, dehydration and stuporous condition resembles that seen in the most advanced diabetes.²⁶ Studies on the blood serum show that the chlorides may not be lower than normal, that the base concentration (Na, K) may be subnormal, and that the alkali deficit appears to be due to the accumulation of large amounts of organic acids in the blood, the major portion of which are ketone acids, but with definitely more than the normal amount of lactic acid.⁴⁷ There seems to be no evidence that the vomiting actually causes acidosis.

To summarize, then, the lowered alkali reserve in the blood which is found in salicylate poisoning is contributed to by one or more of the following factors: 1, Impairment of renal function, as evidenced by retention of urea and non-protein nitrogen; 2, the presence of ketone bodies in the blood, as inferred from the acetonuria almost always occurring; 3, an increase in blood lactic acid; 4, an increase in blood amino-acids.

An attempt to correlate the symptoms and signs with the results of pharmacologic research shows that for the most part the vomiting, rapid respirations, rapid pulse, convulsions, impairment of hearing and vision, and the muscular twitchings are due to the effect of the drug on the central nervous system. The epigastric burning is caused by the direct irritating action of the oil on the gastric mucosa. The Kussmaul respirations, extreme thirst, stupor and coma, and to some extent the rapid pulse and convulsions are due to the acidosis. The marked cyanosis and flushed skin and, to some extent, the increased respirations and rapid pulse are the result of the dilatation of the peripheral blood vessels. Increased blood sugar and acetonuria are evidence of interference with the fat and carbohydrate metabolism.

The treatment, aside from gastric lavage, is symptomatic. The most remarkable recovery on record seems to be that of Case 1. Although this child, as was previously described, was not seen until 24 hours after taking the poison and was then *in extremis* and had a blood CO₂ combining power of 24.9 vol. %, albuminuria, red blood cells and casts in the urine, and a 5+ acetonuria, he recovered. His treatment, specifically, consisted of gastric lavage with 6% sodium bicarbonate and the symptomatic measures of caffeine and adrenalin on arrival, blood transfusions, intravenous glucose and saline, 5% glucose and solid sodium bicarbonate by mouth, 5% glucose and 5% sodium bicarbonate (75 cc. of a mixture of equal parts) by rectum, digitalis, colonic irrigations, and "force fluids by mouth" whenever such was possible. The 2 cases of Olmsted and Aldrich⁴⁶ reacted favorably to intensive alkali treatment, and were also given a glucose hypodermoclysis with 7½ units of insulin. Solid sodium bicarbonate was mixed with orange juice and given by mouth and in this way 5 gm. of the salt were administered to the child in an hour or two.

In the maintenance of renal function lies the best hope of recovery. As has been shown by Morris and Graham,⁴⁵ large doses of alkali more than double the rate of excretion and cause over 90% of the salicyl to be recoverable in the urine. Likewise, they found that in patients given 6 gm. of sodium salicylate and 12 gm. of sodium bicarbonate a day there was no drop in blood CO₂ combining power, no decreased urine output, no abnormal retention of blood constituents, and no evidence of any renal damage. Without the bicarbonate protection there was a decrease of alkali reserve and urine output,

an increase in the blood non-protein nitrogen, and evidences of renal damage in the urine. Johnson³² shows that twice the amount of sodium bicarbonate is necessary to replace the amount of CO_2 lost from the bicarbonate reserve with a given amount of sodium salicylate. Since methyl salicylate is excreted much more slowly and incompletely and withal is definitely more toxic, three or four times as much bicarbonate are indicated. If a poisoning case is seen within 20 to 25 hours a 6% sodium bicarbonate gavage, with several grams of the salt left in the stomach, is a doubly good measure as it not only allows a large intake of the substance but neutralizes the salicylic acid liberated in the stomach. It is likewise obvious that fluids should be forced in every possible manner as long as no contraindications are manifested. Oral and intravenous glucose solution, usually 5% in strength, has contributed some beneficial effect in the cases where it has been used. Its use is supported experimentally by some work of Madisson³⁷ who found, in experiments on dogs which had been given toxic doses of sodium salicylate, that oral and intravenous glucose lessened the degree of the usual impairment of renal function and the subsequent pathologic lesions he claims to find in the kidneys.

In cases of poisoning where there is acetonuria, hyperglycemia, and marked acidosis, intravenous glucose with a very small dose of insulin is indicated, as this measure seems to have an advantageous effect upon that part of the acidosis which is due to impaired carbohydrate and fat metabolism.

Blood transfusion is a good general measure in severe cases and was used with evident success in Case 1.

Enemata and high colonic irrigations are indicated because they will help to evacuate the bowel of what methyl salicylate there may be in the feces, will promote good intestinal elimination, and will clean out the colon so that rectal glucose and bicarbonate solutions may be more readily absorbed.

Also, since anuria was described in 1 or 2 cases in which a full urinary bladder was found at autopsy, catheterization should not be refrained from if there is any possible evidence of retention.

In cases where there is a substantially weak pulse, caffeine and adrenalin may be given to advantage, the former for its cardiac stimulation and the latter for its vasoconstrictor power. If there is a continued weak pulse and feeble heart sounds, digitalis is indicated and has been used to definite advantage. Atropine has proved helpful in relieving respiratory distress.

When the alkali reserve is greatly depleted, intravenous sodium bicarbonate, of a 4% or 5% solution, may be given, but it allows the intake of a relatively small amount of the salt and the actual amount to be given must be carefully considered due to its immediate specific reactivity in the blood. About 13 cc. per kilogram of body weight will raise the CO_2 combining power 15 vol. %. It is safer to

give intravenously a $\frac{1}{2}$ molar solution of sodium lactate, and 60 cc. per kilo will raise the CO_2 combining power about 30 vol. %. Excellent results have been obtained from the use of this salt in treating acidosis at the Harriet Lane Home. There is no reason to believe that this salt would have any deleterious effect upon the metabolism or excretion of the slightly increased lactic acid which has been found in the blood in salicylate poisoning.

As far as combating the general systemic effects of the salicyl ion is concerned, three things may be done: To remove the source of supply of the poison—gavage, emesis, and enemata; to promote its excretion—give fluids, sodium bicarbonate and glucose; to replenish the alkali reserve—give the above mentioned sodium salts.

Since the mortality in this type of poisoning is 59%, and that of bichloride of mercury poisoning is 25 to 50%,³⁹ it seems reasonable that steps should be taken toward its prevention; 41% of the methyl salicylate poisonings occurred accidentally in children under 5 years of age. Thus, if bottles of oil of wintergreen were labelled "Poisonous if taken internally," it would serve to remind parents to keep them under lock and key.

Summary. 1. Three new cases of oil of wintergreen poisoning are reported, and 20 cases hitherto not included in the lists of reported cases were found in the literature. These, with the other known cases, a total of 46, have been summarized. Thirteen autopsy reports were found in the literature, and these, with that of 1 of the author's cases, are summarized. The mortality is found to be 59%, while 41% of the poisonings occurred in infants.

2. The typical case clinically was found to have early vomiting, rapid and deep respirations, rapid pulse, cyanosis, flushed skin and extreme thirst. Then, in the fatal cases, followed stupor, coma, impaired vision and hearing, convulsions, and exodus in respiratory failure. The blood studies showed an average CO_2 combining power of 32.7 vols. %, a non-protein nitrogen of 70.2 mg. %, and a sugar of 152 mg. %. The urine showed a 4+ acetoneuria and a positive test for salicylate in all those tested; 60% of the tests for albuminuria were positive. Many urines showed red blood cells and casts.

3. There are no remarkable anatomic pathologic changes, and those which are found are not typical or specific in any way. The chemical changes in the blood and the known pharmacologic properties of the drug indicate that the pathologic physiologic changes are more striking than the anatomic ones. The renal function impairment and the lowered alkali reserve in the blood ("acidosis"), the central nervous system depression, and the interference with the carbohydrate, fat, and nitrogen metabolism are the most important changes.

4. The literature on the pharmacology of methyl salicylate is reviewed with the purpose of correlating the findings and applying them therapeutically. The "acidosis" is found to be mostly a com-

compensated fixed acid acidosis, and is due to retention, by damaged kidneys, of urea and non-protein nitrogen, to an increase in blood amino acids, in blood lactic acid, and to a ketonemia. These last two abnormalities are apparently the result of impaired carbohydrate and fat metabolism; they are also due, to some extent, to protracted vomiting when it occurs.

5. There is conclusive evidence to the effect that the ingestion of 2 to 4 times as much sodium bicarbonate as methyl salicylate helps to prevent the toxic action of the latter and to speed up its excretion and make it more complete. Also, glucose, probably through its diuretic property, has a definite protective effect upon the kidneys in salicylate poisoning.

Aside from an initial thorough gastric lavage, the treatment is symptomatic. One of the chief aims is to protect the kidneys, for in the maintenance of their function lies the chief hope of recovery. This can be done through the ample administration of fluids; calcium lactate and glucose solutions should be given intravenously. Immediate sodium bicarbonate gavage, enemata, and proctoclyses are imperative, and this salt should be administered by mouth in ample amounts. Atropine, caffeine, adrenalin, blood transfusions, and in some cases digitalis are of benefit. If hyperglycemia is discovered, a small dose of insulin given simultaneously with intravenous glucose is beneficial.

6. Since 4 cc. of oil of wintergreen has been lethal in an infant and 6 cc. lethal in an adult, and in view of the high mortality of 59%, it has been suggested that the drug be labelled "Poisonous if used internally."

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THE CLINICAL SIGNIFICANCE OF SERUM PROTEINS IN HEPATIC DISEASES.

COMPARED WITH OTHER LIVER FUNCTION TESTS.

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MANY investigators have noted alterations in the concentration of the serum proteins during the course of cirrhosis and other types of hepatic disease.^{2,3,12,25} A reduction in the serum albumin has been most frequently recorded; the serum globulin is often

elevated and the albumin-globulin ratio reversed according to many observers.

Kerr, Hurwitz and Whipple¹⁵ noted that hepatic necrosis produced by phosphorus and chloroform was associated with lowering of the level of the blood proteins and that liver injury delayed the regeneration of proteins depleted by plasmapheresis. Sawada²² and also Henriques and Klausen⁹ reported that hepatic damage or ligation of the common duct was followed by a decrease in the albumin and an increase in the globulin. The frequent occurrence of hypoalbuminemia in both clinical and experimental liver injury indicates that the liver is concerned with either the manufacture of albumin or the maintenance of its proper level in the blood. It has been suggested that the protein decrease may be due to nutritional disturbances,^{25c} defective protein formation,^{25c, d} lack of reserve protein-building material normally stored in the liver,^{10, 15} loss of albumin into the ascitic fluid^{25f} or increased capillary permeability causing escape of protein into the tissues.¹⁴ It is evident that further investigation is necessary in order to explain fully the mechanism of serum-protein changes in hepatic disorders.

During the past 4 years we have had the opportunity to study the serum albumin and globulin levels in 45 patients with various hepatic diseases.* This group was composed of the following:

	No. of cases.
Portal cirrhosis	12
Non-obstructive biliary cirrhosis	2
Obstructive biliary cirrhosis	6
Toxic cirrhosis (Mallory)	2
Banti's syndrome with hepatic involvement	2
Metastatic malignancy of the liver	3
Generalized tuberculosis with hepatic involvement	2
Acute hepatocellular damage of various types	10
Obstructive jaundice	6

Serum Proteins in Portal Cirrhosis. In the group of 12 patients with portal cirrhosis (Table 1), a total of 24 determinations of the serum proteins were made. In every instance the albumin was below our accepted low normal of 4.5 gm. %, being 3.5 or less in all but 1 of the specimens examined. A level of 3.97 gm. was obtained in a man (J. F.) without any clinical manifestations of liver dysfunction in whom a small hob-nail liver was discovered at operation for a duodenal ulcer. Repeated determinations over periods as long as 6 months suggest that, when the patient with portal cirrhosis develops a definite hypoalbuminemia, the chance of a subsequent sustained increase in this protein is slight. There seems rather to be a trend downward in the albumin content of the blood in the advanced cases as the disease process continues. However, symptoms antedated our first examinations for periods

* The determinations were made by a modification of Howe's method, as described by Hawk and Bergem.⁷

that varied from 4 weeks to 2 years, yet the serum albumin was not lower in those patients who had been ill for longer periods before admission. Hypoalbuminemia was noted before the development of ascites in 3 of these patients.

The increase in serum globulin in portal cirrhosis noted by others was not as constant in this series as the lowering of the albumin level. In our laboratory the normal range of globulin is regarded as between 1.5 and 2.5 gm. %. The globulin was above this level

TABLE 1.—SERUM PROTEIN AND LIVER FUNCTION DETERMINATIONS IN PORTAL CIRRHOSIS.

Patient.	Date.	Total protein.	Albumin.	Globulin.	A/G.	Ascites.	Takata reaction.	Galactose.	Bromsulphalein.	Urobilinogen.	Van den Bergh.
J. F.	1/ 3/35	6.09	3.97	2.12	1.87	Neg.	Neg.	2.40	18%	1/60	0.2
C. DeM.	11/ 6/34	5.30	2.24	3.06	0.73	Pos.	Pos.	3.72	18%	...	1.0
N. C.	11/12/32	6.56	2.57	3.98	0.64						
M. M.	5/ 1/35	5.15	2.94	2.21	1.33	Pos.	Pos.	2.98	70%	1/10	7.5
	5/18	5.68	3.07	2.61	1.17	Pos.	Pos.	..	60%	...	3
	5/29	6.84	2.94	3.90	0.75	Pos.					
E. B.	6/29/34	5.46	2.94	2.52	1.16	Pos.	..		50%	1/60	0.2
	10/24	4.90	2.17	2.73	0.79	Pos.	Pos.	1.53	45%	1/40	0.2
	11/13	6.09	2.85	3.24	0.87	Pos.	Pos.	..	8%	1/60	0.2
	12/11	5.00	3.00	2.00	1.50	Pos.	Neg.				
B. H.	12/29/35	6.90	3.50	3.40	1.03	Pos.	..		30%	...	4
	1/31/36	7.00	2.20	4.80	0.45	Pos.	Pos.	2.04	60%	...	1.5
	2/19	5.10	1.70	3.50	0.48	Pos.					
M. D.	7/26/35	6.06	3.35	2.71	1.23	Pos.	Pos.				
J. R.	2/12/36	6.34	2.94	3.40	0.86	Neg.					
A. R.	4/11/36	6.09	3.14	2.95	1.06	Pos.	Pos.	1.79	33%	1/30	3
H. F.	8/31/34	9.22	3.33	5.89	0.56	Neg.	Pos.	4.60	8%	1/40	0.45
	12/ 5	5.59	3.39	2.20	1.54	Pos.	Pos.	7.37	..	0	9.0
	12/11	4.96	1.78	3.18	0.55	Pos.	Pos.	12.0
	12/18	4.61	2.58	2.03	1.27	Pos.					
A. K.	3/19/35	5.46	3.23	2.23	1.44	Pos.	Neg.	..	55%	1/40	1.2
	4/ 3	5.09	3.17	1.92	1.65	Pos.	..	1.48	35%	1/80	0.5
	5/11	5.67	3.03	2.64	1.14	Pos.					
S. W.	3/26/35	5.61	3.13	2.48	1.26	Pos.	Neg.	4.30	45%	...	0.9
Range	...	4.61- 9.22	1.7- 3.97	1.92- 5.89	0.45- 1.87						

Total protein less than 6.5 in 19
 Albumin less than 4.5 in all
 Albumin less than 3.6 in 23
 Globulin more than 2.5 in 16
 Alb./glob. less than 1.0 in 10
 Alb./glob. less than 1.5 in 20

Of 24 determinations.

in 16 of the 24 determinations. Usually the decrease in albumin was greater than the increase in globulin, so that the total protein was below the normal limit of 6.5 gm. % in 19 instances. Indeed every patient showed an hypoproteinemia at some time during the period of observation except Case N. C.

Our findings suggest that the diagnostic value of the reversal of the albumin-globulin ratio has been somewhat overemphasized. In the 24 determinations upon these patients with portal cirrhosis, the ratio was less than 1.5 twenty times, being below 1 in ten of these. The globulin level was more variable than that of the albumin.

The ratio of the two proteins to each other fluctuated a great deal during the course of the disease without any striking change in the serum-albumin content, and without there being any apparent variation in the associated liver disturbance.

TABLE 2.—SERUM PROTEIN AND LIVER FUNCTION DETERMINATIONS IN NON-PORTAL CIRRHOSIS OF VARIOUS TYPES.

Patient.	Date.	Total protein.	Albumin.	Globulin.	A/G.	Ascites.	Takata reaction.	Galactose.	Bromsulphalein.	Urobilinogen.	Van den Bergh.
<i>Toxic Cirrhosis.</i>											
P.B. . .	7/19/34	6.40	1.39	5.01	0.27	Pos.					
	7/25	2.65	1.35	1.30	1.03	Pos.	Pos.	6.84	23%	1/80	0.9
	8/27	7.66	2.56	5.10	0.50	Pos.	Pos.	5.35	45%	1/80	0.65
	10/9	6.80	2.70	4.10	0.65	Pos.					
	11/19	5.31	2.75	2.56	1.08	Pos.	Pos.	..	45%	1/325	0.7
J.S. . .	11/22/32	8.28	4.06	4.22	0.96	Pos.	..	5.64	75%	1/10	15.0
	1/ 3/33	6.56	2.84	3.72	0.76	Pos.	..	6.43	..	1/40	1.75
	1/20	4.84	2.52	2.32	1.08	Pos.	..	3.13	1.2
	2/15	6.15	2.37	4.28	0.55	Pos.	..	1.07	0.5
<i>Non-obstructive Biliary Cirrhosis.</i>											
L.M. . .	2/ 5/35	7.97	3.99	3.98	1.00	Neg.	Pos.	..	50%	1/140	1.2
	5/7	6.41	3.72	2.69	1.39	Neg.	Pos.	..	25%	1/50	2.4
	4/ 7/36	8.47	4.99	3.48	1.41	Neg.	Pos.	..	50%	1/50	3.2
N.W. . .	2/ 4/36	5.00	2.56	2.44	1.04	Neg.	Pos.	2.47	60%	1/10	16.0
	2/18	5.86	3.14	2.72	1.15	Pos.	Pos.	1/10	18.0
	3/17	5.22	2.56	2.66	0.96	Pos.	Pos.	13.5
<i>Obstructive Biliary Cirrhosis</i>											
E.O'N. .	1/22/35	5.96	3.09	2.87	1.08	Neg.	Pos.	..	20%	1/60	1.3
	2/26	4.18	1.78	2.40	0.70	Pos.					
S.H. . .	4/13/35	4.69	2.40	2.29	1.04	Neg.	Pos.	..	50%	1/60	9.0
A.P. . .	2/17/36	5.78	2.53	3.25	0.79	Neg.	Neg.	2.89	40%	1/20	8.25
	3/24	8.59	4.88	3.71	1.30	Neg.	Neg.	1.10	6%	1/10	0.8
S.G. . .	1/13/36	5.40	3.30	2.10	1.57	Pos.	Pos.	..	30%	..	5.0
H.M. . .	11/ 8/34	5.28	2.55	2.73	0.93	Pos.					
M.S. . .	12/ 6/35	4.40	2.30	2.10	1.09	Neg.	Neg.	Whole urine	14.4
Range	2.65-8.59	1.35-4.99	2.10-5.10	0.27-1.57						

Total protein less than 6.5 in 16
 Albumin less than 4.5 in 21
 Albumin less than 3.6 in 18
 Globulin more than 2.5 in 16
 Alb./glob. less than 1.0 in 10
 Alb./glob. less than 1.5 in 22

} Of 23 determinations.

Serum Proteins in Other Types of Cirrhosis. (Table 2.) We have included 2 men who suffered with the toxic cirrhosis described by Mallory.¹⁸ One of these (P. B.) entered the hospital because of marked ascites of recent onset, giving a history of painless icterus of 3 weeks' duration, 5 months previously. On admission the serum albumin was 1.39 gm. %. During the succeeding 5 months of his life, the albumin varied between 1.35 and 2.75 gm. %, but the globulin fluctuated markedly. The first 2 protein determinations, 6 days apart, may be cited to illustrate this. The albumin was practically constant but the globulin dropped from 5.01 to 1.3, changing the albumin-globulin ratio from 0.27 to 1.03. This

occurred without any demonstrable clinical change and serves to illustrate the tremendous variations which may occur in serum globulin and in the albumin-globulin ratio within brief periods. The other patient with toxic cirrhosis (J. S.) is also of interest because the first examination, 1 month after the onset of his illness, showed the albumin to be only slightly decreased to 4.06 despite very marked jaundice and a positive galactose test. As the illness continued, however, the albumin dropped considerably and reached the low level of 2.37 gm. % after 3 months.

The 2 patients with biliary cirrhosis of the non-obstructive variety both showed albumin deficiency. In 1 of these (L. M.) it was slight and tended to improve. In the other case (N. W.) the albumin decrease was more marked until the patient's death.

TABLE 3.—SERUM PROTEIN AND LIVER FUNCTION DETERMINATIONS IN BANTI'S SYNDROME.

Patient.	Date.	Total protein.	Albumin.	Globulin.	A/G.	Takata reaction.	Bromsulphalein.	Urobilinogen.	Van den Bergh.	
M. L.	...	11/20/34 4/ 6/35 4/ 4/36	6.63 6.47 5.78	3.35 4.69 4.38	3.28 1.78 1.40	1.20 2.63 3.10	Neg. Neg. Neg.	18% 25% 20%	1/90 1/80 1/20	1.4 0.9
J. A.	...	9/ 6/32 12/14/35 2/25/36 3/30 4/21	8.59 6.99 5.78 5.10 6.72	5.07 4.11 2.67 3.57 3.61	3.52 2.89 3.11 1.59 3.11	1.44 1.42 0.85 2.25 1.16	Neg. Neg. Pos. Pos. Pos.	15% 20% 0 14% 12%	1/40 1/20 1/20 1/30 1/20	0.4 1.2 0.3 0.7 0.7
Serum Protein and Liver Function										
M. B.	...	2/16/35 4/13	7.53 7.65	3.02 3.42	4.51 4.23	0.67 0.80	Pos. Pos.	9% 6%	1/60 1/100	Less than 0.2 Less than 0.2
J. L.	...	1/29/35	5.46	2.90	2.56	1.13	Neg.	18%	1/100	0.5
Serum Protein and Liver Function Determinations in Metastatic Malignancy										
	Location, original neoplasm.									
M. C.	Cervix	2/14/35	6.33	3.68	2.65	1.39	Neg.	40%	1/150	2.4
C. H.	Stomach	1/ 7/35	5.75	2.87	2.85	1.00	Pos.	28%	1/40	0.4
H. L.	Stomach	1/29/36 3/30	7.50 5.15	3.97 3.52	3.53 1.63	1.12 2.15	Neg. Pos.	20% 24%	1/40 1/20	0.6 1.2

All 6 cases with biliary cirrhosis developing secondary to long-standing common-duct obstruction showed marked albumin deficiency. In 1 of these a low-albumin level on admission returned to normal after 5 weeks, coinciding with improvement in the clinical status and in other liver function tests. In another patient (E. O'N) the initial albumin level was 3.09 gm. %. During the following month she suffered a number of hemorrhages and, although she received many transfusions, when the blood was reexamined 1 month later it was found that the albumin had decreased to 1.78 gm. %. It is possible that this is a clinical counterpart of the experimental findings of Kerr, Hurwitz and Whipple who found that animals with damaged livers were unable to restore protein lost by bleeding.

Serum Proteins in Other Types of Chronic Diffuse Liver Disease. (Table 3.) The serum-protein behavior in 2 cases having the so-called Banti's syndrome is of interest. One (J. A.) was seen originally in September, 1932, with marked ascites and moderate splenomegaly. The bromsulphalein test was positive, although the serum albumin was normal. He was lost to us until December, 1935, when he appeared with persistent ascites, dye retention and now an hypoalbuminemia. Since splenectomy in January, 1936, progressive liver change is suggested by further decrease in serum albumin and persistence of evidence of liver dysfunction.

This case can be compared with M. L. whose splenectomy was performed in March, 1933, before signs of liver dysfunction appeared. Twenty months later the bromsulphalein test first became positive and the albumin level dropped to 3.28 gm. %. Subsequent examinations at 5 months and 1 year showed persistent retention of bromsulphalein but normal serum proteins. A study of these cases suggests that the liver's function of removing dye from the blood stream is impaired first and is more permanent in Banti's syndrome than is an alteration in the serum proteins. It seems probable that alteration in the serum proteins does not occur in Banti's syndrome until hepatic changes become advanced.

We have included serum-protein studies in 2 patients with generalized tuberculosis who at autopsy showed extensive involvement of the liver. The hepatic damage had been suggested during life by the abnormal response to the function tests used. In both of these cases the albumin was decreased and 1 there was marked elevation of the globulin. To ascribe these changes entirely to the liver injury would probably be unjustified, since in both there were definite nutritional deficiencies. The albumin decrease, however, is similar to that found in other types of hepatic disease.

Three patients with metastatic malignancy of the liver also showed a lowering of the blood albumin. Malnutrition may have been somewhat responsible in 2 cases with a primary neoplasm in the stomach. In both of these, however, a widespread destruction of the liver was found at necropsy.

Serum Proteins in Acute Hepatocellular Damage. (Table 4.) Alterations in the serum proteins are not confined to the chronic hepatic disorders.^{25a, i} Determinations were recorded in 3 cases of toxic hepatitis, 6 of so-called catarrhal jaundice and 1 of cholangitis. A fatal case of cinchophen hepatitis and a case of subsiding arsenical jaundice showed hypoalbuminemia. The protein behavior in a man who died of chloroform poisoning was unusual. The first albumin level, 4 days after the onset, was 2.85 gm. % which rose to the normal level of 4.56 just before death 2 days later. The globulin readings were low and the albumin-globulin ratio normal.

Six patients with so-called catarrhal jaundice are included. The albumin was reduced in 5 and the globulin elevated in 4 patients.

In 1 of the patients (S. S.) the albumin returned almost to normal after 2 days as the jaundice decreased and the clinical course improved. The remaining patient in this group of acute disturbances was a man with cholangitis and multiple liver abscesses, in whom nutritional factors may have been at least partly responsible for the low albumin without appreciable increase in the globulin.

TABLE 4.—SERUM PROTEIN AND LIVER FUNCTION DETERMINATIONS IN ACUTE HEPATOCELLULAR DAMAGE.

Patient.	Diagnosis.	Date.	Duration.	Total protein.	Albumin.	Globulin.	A/G.	Takata reaction.	Galactose.	Bromsulphalein.	Urobilinogen.	Van den Bergh.
N. K.	Cinchophen hepatitis	5/ 4/35	2 wks.	5.16	2.76	2.40	1.15	Pos.				
H. S.	Chloroform poisoning	2/20/33	4 days	4.27	2.85	1.42	2.00	1/30	20
E. E.	Subeiding arsenical hepatitis	2/22/33 2/13/35	6 days 2 mos.	5.66 7.25	4.56 3.74	1.10 3.51	4.14 1.06	.. Neg.	..	90% 6%	..	30 0.7
B. S.	"Catarrhal jaundice," lues	6/ 2/34	20 days	5.22	2.50	2.72	0.91	Pos.	5.6	..	1/10	4.0
S. S.	"Catarrhal jaundice"	9/10/34	12 days	5.25	2.16	3.09	0.69	Neg.	1.5	..	1/100	10.0
T. W.	"Catarrhal jaundice," lues, alcoholism	9/12/34 11/25/35 12/ 2/35	14 days 10 days 17 days	6.31 7.65 10.03	4.16 4.49 5.52	2.14 3.16 4.51	1.94 1.42 1.22	.. Neg. ..	1.92 4.44 30% 1/40 1/20	7.5 6.0 1.2
B. M.	"Catarrhal jaundice," lues	12/19/35	2 wks.	7.66	4.30	3.36	1.28	Neg.	6.49	20%	..	1.5
W. M.	"Catarrhal jaundice"	7/22/35	7 days	5.20	3.00	2.20	1.36					
E. P.	"Catarrhal jaundice"	1/21/36	7 days	5.22	3.14	2.08	1.51	Pos.	2.453	..	1/100	3.0
J. Q.	Cholangitis, multiple hepatic abscesses	4/28/34	1 mo.	5.31	2.94	2.37	1.24	7%	..	0.3
Range	4.27-10.03	2.16-5.52	1.10-4.51	0.69-4.14					

Total protein less than 6.0 in 8
Albumin less than 4.5 in 11
Albumin less than 3.6 in 7
Globulin more than 2.5 in 6
Alb./glob. less than 1.0 in 2
Alb./glob. less than 1.5 in 9

Of 13 determinations.

In these cases of acute hepatocellular damage the globulin levels were lower, and the albumin-globulin ratio less altered than in the cirrhoses. The tendency toward lowering of the albumin level seemed to be greater in those whose illness was more severe. Improvement in the serum-albumin level was not invariably a favorable prognostic sign.

Serum Protein in Obstructive Jaundice. (Table 5.) In 2 cases with carcinoma of the head of the pancreas the albumin was quite low. This may have been due in some measure to the malnutrition of malignant disease as suggested by Peters and Eisenman.²² Three

of 4 patients with common-duct stone obstruction of 10 days', 3 weeks' and 3 months' duration, had moderate lowering of the albumin. The levels of the albumin were not decreased in relation to the duration of the jaundice. In the fourth case of incomplete obstruction of 3 months' duration, the albumin reading was practically normal. Our findings in obstructive jaundice suggest that the protein changes are dependent more upon the completeness of the obstruction than upon the duration of the icterus.

Discussion. Analysis of these clinical data does not justify definite conclusions concerning the mechanism of the alteration in the serum proteins in advanced liver disease. The changes were not

TABLE 5.—SERUM PROTEIN AND LIVER FUNCTION DETERMINATIONS IN OBSTRUCTIVE JAUNDICE.

Name.	Diagnosis.	Date.	Dura- tion.	Total protein.	Albumin.	Globulin.	A/G.	Takata reaction.	Galactose.	Bromsulphalein.	Urobilinogen.	Van den Bergh.
M. L.	Carcinoma, head of pancreas	1/13/35	6 mos.	4.156	2.09	2.07	1.01	Neg.	0	14
G. G.	Carcinoma, head of pancreas	10/18/34	3 mos.	4.00	1.80	2.20	0.81	..	0.17	98%	Whole urine	2.6
W. W.	Common duct stone	4/16/35	10 days	6.15	3.33	2.82	1.18	Neg.	2.60	35%	Whole urine	6.0
E. G.	Common duct stone	1/ 7/36	3 wks.	6.72	3.72	3.00	1.24	Neg.	2.0
S. T.	Common duct stone	11/19/35	3 mos.	5.34	3.88	1.46	2.65	Neg.	0	2.4
J. L.	Common duct stone	1/ 9/36	3 mos.	6.93	4.46	2.47	1.80	Neg.	0.818	18%	Whole urine	0.7
Range	4.00- 6.93	1.80- 4.46	1.46- 3.00	0.81- 2.65					

Total protein less than 6.0 in 3 }
 Albumin less than 4.0 in 5 }
 Globulin more than 2.5 in 2 } Of 6 determinations.
 Alb./glob. less than 1.0 in 1 }
 Alb./glob. less than 1.5 in 4 }

due in most instances to an inadequate protein intake. However, we cannot affirm or deny the rôle of faulty absorption of proteins from the alimentary canal. The strongest argument against this factor is the rapidity with which serum-protein changes occur in acute diffuse types of liver disease. Increased metabolism played no part in the serum-protein changes in these cases. A study of our material justifies the statement that protein loss *viâ* ascitic fluid is not an important initial cause of hypoalbuminemia. Indeed, it seemed more likely that the reduction in serum albumin may have been responsible to some extent for the abdominal fluid. Hypoalbuminemia was often present in chronic liver disease in the absence of ascites. In most of the acute cases the alteration in blood protein was not associated with peritoneal fluid. It was

often impossible to maintain a normal protein level in chronic cases in spite of an adequate protein supply in the form of blood transfusions or plasma infusions (as suggested by Strumia and Monaghan). Protein loss into the ascitic fluid could not be held responsible in some instances. Therapy was successful in maintaining an adequate protein level only in those cases in which liver function improved as measured by other liver-function tests. The evidence at hand both clinical and experimental favors some fault in liver function *per se* to account for the alteration in blood proteins in hepatic disease. Whether this defect is due to inability to manufacture or synthesize the protein or to ineffectual mobilization remains to be determined.

Serum-protein Levels Compared With Various Liver-function Tests.—This type of comparison was attempted by Alca,^{23a} who concluded that a definite parallel existed between albumin decrease and hepatic insufficiency and also by Lupu and Papazian,¹⁶ who

TABLE 6.—COMPARISON OF THE SERUM ALBUMIN LEVEL AND THE RESULTS OF LIVER FUNCTION TESTS.

Little Liver Disease.									
Cirrhosis of Various Types.									
Albumin.									
De-Nor.									
creased. ml.									
Galactose									
Pos. Neg.									
2	1	0	2	0	3	0	2	0	0
Albumin.									
De-Nor.									
creased. ml.									
Urobilinogen									
Pos. Neg.									
4	1	0	1	0	10	0	4	0	0
Bromsulphalein*									
Pos. Neg.									
2	0	0	3	0	17	0	0	0	0

* Including both jaundiced and non-jaundiced cases.

reported that changes in protein metabolism were definitely related to variations in the liver function as measured by carbohydrate tolerance. We will first present a consideration of the albumin levels in relation to the results of the galactose tolerance, bromsulphalein and urine urobilinogen tests in patients with cirrhosis and acute hepatocellular damage. The results of the various tests which have been tabulated correspond to the time of making the serum-protein determinations.

Galactose Tolerance Test. Of 13 patients with cirrhosis and hypopalbuminemia who had 1 or more galactose tolerance tests performed (Tables 1, 2 and 6), 10 had a positive response, if an excretion of 2 gm. or more of the sugar after taking a 40-gm. dose is regarded as positive.^{1,26} In 3 cases of cirrhosis (all portal) the galactose test was negative, although the albumin was decreased quite as low as in those with positive galactose tests. In the patient (A. P.) with obstructive biliary cirrhosis clinical improvement was associated with a rise in albumin and a return of the previously positive galactose test to normal. However, J. S., with a toxic cirrhosis, showed a steady decrease in albumin during the period that the galactose response became normal.

In 4 of 5 patients with acute liver damage the galactose response was positive (Tables 4 and 6). The serum-albumin was essentially normal in 2 of these and definitely below normal in the remaining 2 cases. The fifth case with a normal galactose tolerance had only a mild catarrhal jaundice (S. S.). His albumin was at first quite low but returned to slightly below normal 2 days later. This comparison suggests that the serum albumin is a less delicate index of acute hepatic damage than the galactose test, but that the albumin determination is the more accurate of the two procedures in indicating the presence of a chronic hepatic disorder. The negative results of the galactose test in chronic liver disease are readily explained by the regeneration in many instances of some functioning tissue, which is apparently inadequate to carry on the protein function.

Urobilinogen Test. Simultaneous urine urobilinogen tests and serum-protein determinations were performed in 14 patients with hypoalbuminemia in the cirrhotic group (Tables 1 and 6). If one considers that a reaction to Ehrlich's aldehyde reagent in urine dilutions of greater than 1 to 20 parts is abnormal, then the test was positive in 10 of these 14 patients. The remaining 4 patients were deeply jaundiced at the time of the examinations.

The urobilinogen test was positive in 5 of the 6 patients with hepatocellular damage upon whom simultaneous protein determinations were available (Tables 4 and 6). In 4 of them albumin was likewise diminished. In the other 1 it was normal. In the 1 instance in which the urobilinogen was normal the albumin was definitely reduced. Excluding cases with jaundice, however, the urobilinogen test was positive in every case in which the serum albumin was reduced both in cirrhosis and in acute hepatocellular damage. In cases with deep jaundice, hypoalbuminemia may frequently suggest definite impairment of liver function, which, of course, cannot be determined by the urobilinogen test as long as bile does not gain access to the bowel or infection arise within the bile channels.

Bromsulphalein Test. It is somewhat more difficult to evaluate the bromsulphalein test in terms of liver dysfunction in the presence of jaundice, which may be obstructive in type. The test was performed in 17 patients with cirrhosis and hypoalbuminemia (Tables 1, 2 and 6). In 7 cases the positive response to the dye test was apparently not dependent on jaundice. The 10 other patients, who were tested with bromsulphalein, were jaundiced and, of course, none excreted the dye normally. Even if one ignores the influence that icterus may have on dye retention and considers that all of these positive bromsulphalein reactions were due to the liver damage, the level of the serum albumin would seem to be at least as accurate a measure of hepatic dysfunction as the bromsulphalein test, since a low albumin was found in each patient who had dye

retention. However, the dye test occupies a somewhat superior place in the diagnosis of cirrhosis without jaundice, since extra-hepatic disorders will occasionally cause hypoalbuminemia whereas marked bromsulphalein retention in the absence of icterus is practically pathognomonic of intrahepatic disease.

The bromsulphalein and serum protein determinations were used in 5 patients with acute liver-cell diseases (Tables 4 and 6). The comparison is only of value in 2 of them without clinical icterus. Both showed dye retention and hypoalbuminemia.

Takata Test. Since Jezier's first use, in 1930, of the Takata reaction in the diagnosis of cirrhosis,^{12a} numerous contributions on the subject have appeared.^{4,8,11,12b,17,20,21,24,27} The consensus of opinion has been that the test is positive in the majority of patients with cirrhosis and that it may be positive in other types of advanced liver disease, including severe acute hepatocellular damage. The

TABLE 7.—THE RESULTS OF THE TAKATA REACTION IN RELATION TO THE SERUM PROTEIN LEVEL. (54 DETERMINATIONS IN 37 PATIENTS.)
Takata Positive (32 Tests).
Takata Negative (22 Tests).

Albumin	Globulin	Alb./Glob.
$\left\{ \begin{array}{l} \text{Average, 2.97} \\ \text{Range, 1.35-4.99} \\ \text{Less than 3.6 in 28} \\ \text{More than 3.6 in 4} \end{array} \right.$	$\left\{ \begin{array}{l} \text{Average, 2.96} \\ \text{Range, 1.30-5.89} \\ \text{Less than 2.5 in 10} \\ \text{More than 2.5 in 22} \end{array} \right.$	$\left\{ \begin{array}{l} \text{Average, 1.09} \\ \text{Range, 0.45-2.25} \\ \text{Less than 1.0 in 11} \\ \text{1.0-1.5 in 10} \\ \text{More than 1.5 in 5} \end{array} \right.$
$\left\{ \begin{array}{l} \text{Average, 3.54} \\ \text{Range, 2.09-4.88} \\ \text{Less than 3.6 in 10} \\ \text{More than 3.6 in 12} \end{array} \right.$	$\left\{ \begin{array}{l} \text{Average, 2.70} \\ \text{Range, 1.46-3.53} \\ \text{Less than 2.5 in 9} \\ \text{More than 2.5 in 13} \end{array} \right.$	$\left\{ \begin{array}{l} \text{Average, 1.38} \\ \text{Range, 0.69-2.65} \\ \text{Less than 1.0 in 2} \\ \text{1.0-1.5 in 16} \\ \text{More than 1.5 in 4} \end{array} \right.$

nature of the reaction remains in doubt. Jezier felt that the results varied with the globulin content of the serum, becoming positive when this protein became relatively excessive. This seemed incompatible with the negative findings in such diseases as nephrosis. Other investigators have concluded that while there is usually some lowering of the albumin and elevation of the globulin in the positive reacting sera, that these are not constant findings.^{3,17,21} Other theories, advanced to explain the reaction, include the supposed presence in the blood of certain fatty acids,²² the accumulation of ammonia because of liver dysfunction,¹⁷ and increase in some of the individual globulin fractions.^{2,11}

It is not our purpose at this time to present in detail our experience with the Takata reaction as a diagnostic measure. The tables show that the Takata reaction was positive in a high percentage of cases with severe chronic liver disease, that it was not specific for cirrhosis of any kind, that it was positive in some cases of acute hepatocellular damage, but that it may be negative even in the presence of advanced hepatic dysfunction.

In reviewing the serum-protein levels determined at the time of performing the Takata reaction, we found that the test was

positive more frequently when the albumin was decreased and the globulin slightly elevated (Table 7). The albumin-globulin ratios were at a somewhat lower level in the positive Takata group. However, when individual cases were studied there was considerable variation noted in the amounts of albumin and globulin in both the positive and negative reacting sera. Thus, the albumin was found to be less than 3.6 gm. % in 28 of the 32 positive sera but it was also below this level in 10 of the 22 that were negative. The globulin was more than 2.5 gm. % in 22 of those reacting positively but it was also above this amount in 13 of those that were negative. However, there were only 5 cases with a positive Takata reaction who showed a normal albumin-globulin ratio, and in these cases the total protein level was reduced. We are, therefore, forced to conclude that although the serum proteins were abnormal in some respect, in practically every case showing a positive Takata reaction, the mechanism is not entirely dependent upon the ratio of the albumin to the total globulin. It is possible that changes in the concentration of the various globulin fractions may be a responsible factor.

Summary. 1. Serum-protein determinations have been carried out on 45 patients with various types of acute and chronic hepatic disease. Hypoalbuminemia was the most consistent alteration noted, being present at some time in every case of chronic advanced liver disease and in most cases of obstructive jaundice. Elevation in the serum globulin and lowering of the albumin-globulin ratio, although usually present, was not as significant or constant as the reduction in serum albumin.

2. Identical serum-protein changes were noted in some cases of acute hepatocellular damage but not with the same frequency or degree as in the cirrheses.

3. As to the mechanism responsible for the protein changes, our data tend to support the existence of some basic disturbance of liver function to account for the hypoalbuminemia in liver disease.

4. Simultaneous tests of liver function including the galactose, urobilinogen, bromsulphalein and Takata tests were carried out. Their clinical and prognostic values are compared. Further evidence is presented to refute the importance of an inversion of the albumin-globulin ratio *per se* as the mechanism responsible for the positive Takata reaction.

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FURTHER EXPERIENCE IN THE DIAGNOSIS OF HYPERPARATHYROIDISM. A MINIMAL DEGREE OF HYPERPARATHYROIDISM.

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ONE of the objects of the present communication is to emphasize, as brought out in 1934,¹ the commonness and polymorphism of hyperparathyroidism by the report of 18 proved cases from this hospital in addition to the 17 previously reported from the same clinic. An attempt will be made, furthermore, to analyze why the disease is so frequent in this particular clinic. In fact, the stimulus to this paper came from a publication by Wilder and Howells² who, after pointing out that they had been able to collect only 5 cases at the Mayo Clinic in spite of an early and steady interest in the disease, ended by suggesting that the high incidence in Boston and London was due to some regional factor—possibly lack of ultraviolet radiation in hyperparathyroid belts. Although it is admitted that lack of ultraviolet radiation predisposes to rickets, that rickets is associated with parathyroid hyperplasia, and that a pre-existing hyperplasia might predispose to

adenoma formation, there are considerations which make it seem unlikely that lack of ultraviolet light has much to do with the incidence of the disease. In the first place, there does not seem to be a predisposition to the disease among the colored race. It is pretty well established that the negro is more susceptible to rickets because the pigment keeps out the ultraviolet light. Of the 35 cases of hyperparathyroidism in our series only 1 was in a negress and she was almost white. Clinics with large numbers of colored patients have not reported large numbers of hyperparathyroid patients. The rickets belt and the hyperparathyroid belt do not coincide. Furthermore, other clinics in Boston have not had an undue number of cases. It, therefore, seems of interest to analyze the 35 cases to ascertain, if possible, why the series is so large.

The first possibility that would occur to one is that more cases are being sent to this clinic because of its known interest and experience with the condition. The first patient with hyperparathyroidism studied in this country was at this hospital just a decade ago, so that after all this clinic had several years start on other clinics. Of the 35 patients in the series, however, 22 were first suspected of having the disease after entry into the hospital; only 13, including the first patient, were sent to the hospital already diagnosed or partly diagnosed. It is apparent, therefore, that the large series is not entirely explainable on the fact that patients are being sent to this clinic. There remain 22 diagnoses to account for.

Hyperparathyroidism Without Clinical Evidence of Bone Disease. The second factor is that many other clinics have not yet fully appreciated that bone disease is not necessarily associated with hyperparathyroidism. The disease was discovered by Mandl¹⁰ and DuBois⁸ in patients with a marked degree of bone disease; in most physicians' minds the history of the disease is fresh and hyperparathyroidism is almost synonymous with osteitis fibrosa generalisata. Indeed, many investigators believe that the parathyroid hormone acts directly on bone tissue and from this it would follow that bone changes are a *sine qua non* of hyperparathyroidism.^{9,13} In the authors' opinion the hormone does not act directly on bone tissue but rather on the phosphorus and calcium equilibria in body fluids; in the state of hyperparathyroidism these changed equilibria lead to increased losses of calcium and phosphorus in the urine; this situation predisposes to bone disease but does not necessitate it. This point of view involves some theoretical considerations which are beyond the scope of this paper. They were discussed in an unpublished paper presented to the Massachusetts Medical Society (1935) entitled, "Is Hyperparathyroidism Necessarily a Bone Disease?" Regardless of the theoretical points, there is no escaping the important clinical fact that many patients with hyperparathyroidism have no symptoms referable to their skeletons, no evidence of bone disease obtainable by roentgenogram,

no elevation of blood phosphatase, and even no evidence of bone disease obtainable by bone biopsy. The first 3 of these points have been stressed before;² the following case history is illustrative of the patient with marked hyperparathyroidism and not even any microscopic bone changes.

Case Abstract. Patient No. 25* (Al. G. H., No. 340457). The patient, a single, Finnish chauffeur, of 39, entered the hospital on October 4, 1934, because of attacks of right sided pain. He had noted bloody urine with one attack. A retrograde pyelogram showed a right ureteral stone. Past history was non-contributory. The patient had lost 45 pounds by "diet and exercise" during the past 2 years. Physical examination was essentially normal. The stone was removed on October 6, 1934. As with all patients who have a kidney stone, routine serum calcium and serum inorganic phosphorus determinations were done and found to be 11.3 mg. per 100 cc. and 2.3 mg. per 100 cc. respectively. These figures were checked at 12.2 mg. and 2.6 mg. and again at 13.0 mg. and 3.0 mg. These values left no doubt that this patient had hyperparathyroidism of fairly marked degree. Roentgenogram failed to show increased radiability of the skeleton and the serum phosphatase level was normal (3.7 and 3.0 Bodansky units, normal range being 3 to 5 units). On October 27, 1934, Dr. Oliver Cope performed a sub-total parathyroidectomy, tibial biopsy being taken at the same time. The parathyroids were all enormous, 6.8 gm. of tissue being removed (4 normal glands weigh about 0.11 to 0.13 gm.). Figure 1 shows the parathyroid tissue removed; Figures 2 and 3 show low and high power photomicrographs of the tibial biopsy in this patient. It will be noted that the cortex was very thick and showed no rarefaction. Most important of all, however, was the fact that by high power there were no osteoclasts and no fibrosis seen, just fat cells and inactivity (Cp. Fig. 3 with Fig. 4). This demonstrated that bone was not being destroyed. One might otherwise have thought that repair was keeping pace with destruction.

Of the 35 patients in the series, there were 12 who had no clinical or roentgenographic evidence of bone disease. (In only 8 cases was the skeleton involved and not the urological system; in 15 both systems were involved.) Of the 12 cases with no skeletal disease, all but 3 were picked up at the Massachusetts General Hospital. Of these 3, 2 came from clinics intimately associated with this clinic. From this it is apparent that the community at large is not diagnosing hyperparathyroid patients who do not have bone disease. It is of special interest that to our knowledge no case of proved hyperparathyroidism without evidence of bone disease diagnosed during life has as yet been published from other clinics. Venables³ published a case in which he emphasized the absence of bony deformities, but roentgenographic studies showed bone disease. Therefore, to carry on the arithmetic, it seems fair to conclude that the 9 cases without bone disease diagnosed at this hospital would not have been picked up at most other clinics. If one subtracts these 9 from the 22 cases diagnosed here, there remain 13 cases unaccounted for. This is still a high number.

* The patients are numbered according to the chronological order in which the disease was demonstrated by surgery. The same numbers are used in all publications from this clinic dealing with the same individuals.⁴

Patients with bone disease in whom the bone disease was only found after the diagnosis of hyperparathyroidism was established should really be considered with those without bone disease as far as the present discussion is concerned. There were 7 such cases, all diagnosed at this hospital. Subtracting these 7 from the remaining 13 one is left with 6 cases unaccounted for.

Cases With a Minimal Degree of Hyperparathyroidism. There still remains a third factor to explain the high incidence at this

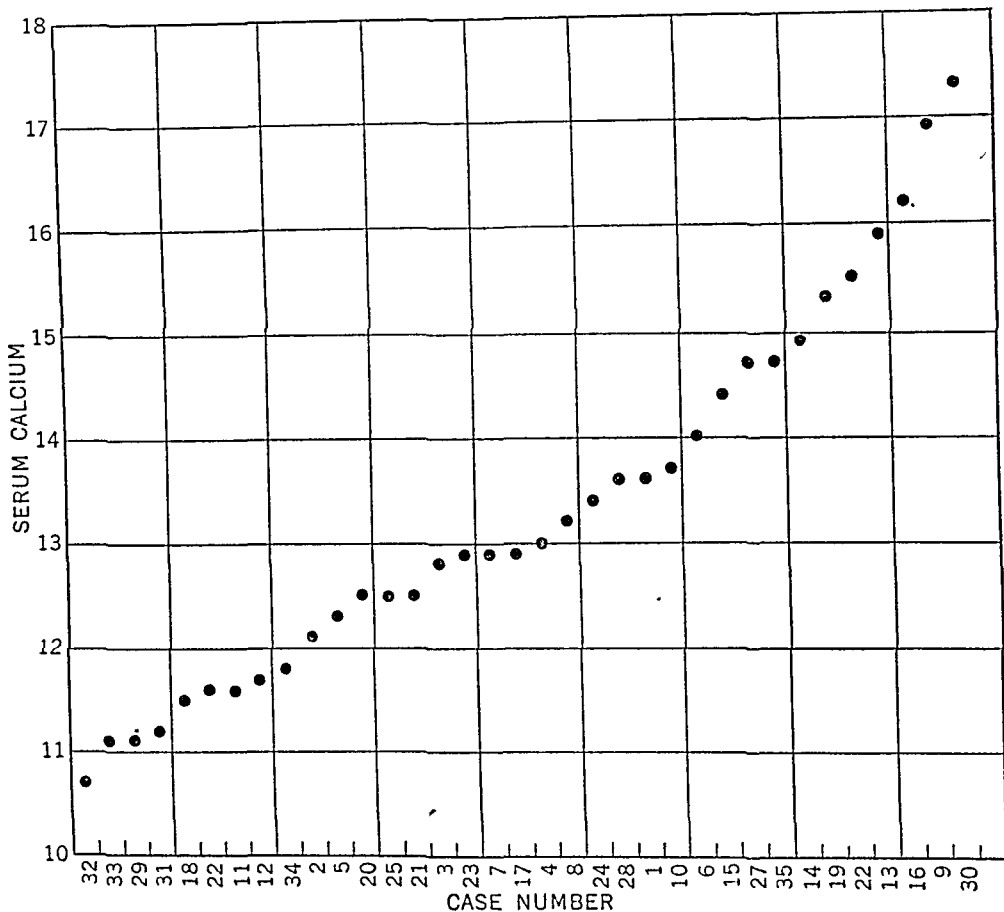


CHART I.—Average pre-operative serum calcium values on first 35 patients at Massachusetts General Hospital with hyperparathyroidism proved by operation.

hospital and that is the diagnosis of patients with a minimal degree of hyperparathyroidism. The nature of the disease is such that it is obvious that there will be cases ranging from a marked degree of hyperparathyroidism all the way down to the normal state. The less the degree of hyperparathyroidism, the less the chemical changes will be from the normal, and the more difficult the diagnosis will be. Shelling¹² gives 12.5 mg. as the lower limit of the serum calcium level in hyperparathyroidism. This figure is too high as is shown by 11 proved cases in this series in each of which the average serum calcium level before operation was below 12.5 mg. (v. Chart I). Most of

these never had values above 12.5 mg.; many others had individual values below 12.5 mg. (v. Chart II). Shelling makes the following statement which requires amplification. "Albright, Aub, and Bauer" described a case, interpreted as hyperparathyroidism, in

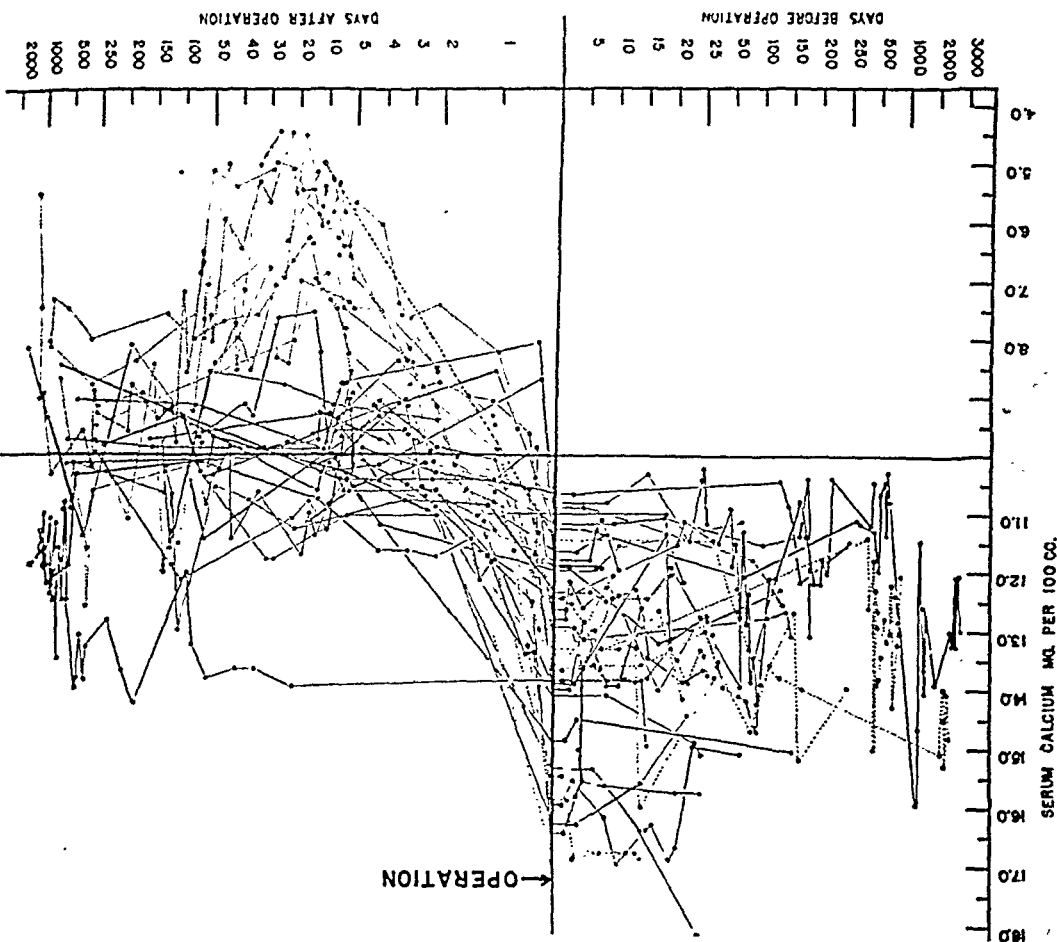


CHART II.—Pre-operative and postoperative serum calcium values on 35 proved cases of hyperparathyroidism from this hospital clinic. Values connected by dotted lines are on patients with high serum phosphatase levels. Final value on each patient is represented by circle instead of dot. Asterisks denote points at which secondary parathyroid operations were done. Note that cases represented by high serum phosphatase levels (and, therefore, having bone disease) are distributed evenly at various levels of hypercalcemia pre-operatively; however, postoperatively these all develop marked hypocalcemia.

which the concentration of calcium in the serum was only 11.5 mg. per cent, but the symptoms consisted only of lassitude, colic, and nephrothiasis, the roentgenogram of the bones showing no evidence of demineralization, the plasma phosphatase remaining within normal limits, and the palpable tumor of the neck being a thyroid, instead of a parathyroid, adenoma." In this patient, No. 12 in

our series, he neglected to add that a parathyroid tumor was found and removed at operation.

In Chart II the pre- and postoperative serum calcium levels are recorded on all 35 cases. From the pre-operative values it is clear that the serum calcium is evenly distributed from values in the normal range all the way up to very high values. It must be emphasized that whereas this borderline group of patients may have a minimal degree of hyperparathyroidism, they still have sufficient to be disabled or killed. Therefore, the discussion of the diagnosis of this group becomes more than an academic question.

If the serum calcium level itself is not sufficiently high to strongly suggest the disease, one can still be lead to the right diagnosis if the serum phosphorus is persistently low (v. infra; Cases 18, 31, 32), or if the calcium excretion is increased in the urine (v. infra; Cases 32, 33), or if the clinical picture fits the disease and no other disease (v. infra; Case 33). In this group, furthermore, it is important to do repeated determinations as the values fluctuate from the normal range into the definitely hyperparathyroid range (v. infra; Cases 31, 32, 33). If the case is one of nephrolithiasis the fact that the stones contain a large amount of calcium phosphate, and that there are no other obvious causes for stones such as infection or obstruction, become additional points in the diagnosis.

There is one other point, which while quite obvious, is so important that it requires a paragraph to itself. In this group of patients where small changes in the serum calcium level are significant, the serum protein determination becomes of the utmost importance (v. infra; Case 32). It has been shown by McLean and Hastings^{11b} that the calcium in the serum is in two states, that in ionized form and that bound to protein. The serum calcium determination measures both together. The amount bound to protein is a function of the amount of protein (as well as of the amount of ionized calcium and pH); the amount of ionized calcium depends on the degree of hyperparathyroidism. Thus the ionized calcium may be slightly high due to a mild degree of hyperparathyroidism, but if at the same time the patient has a low serum protein level, the other fraction will be low, so that the total calcium may end by being normal. It, therefore, becomes necessary to make a correction in the calcium values for low serum protein values. This can easily be done from a linear chart published by McLean and Hastings.^{11b}

Case Abstract. Patient 32 (P. H., No. 36569), a married woman aged 48, of Buffalo, N. Y., consulted the clinic on February 21, 1936, because of bilateral kidney stones. Her first symptoms of nephrolithiasis had developed in 1932. A stone had been removed from the right kidney in 1933. She took large amounts of milk. There were no bone symptoms. Physical examination was non-contributory. Roentgenograms showed multiple bilateral renal calculi and normal appearing bones. The urine showed large amounts of calcium and phosphates to rough tests; no albumin; no bacteria (sterile culture); a few red cells and no white cells. The stones in her right kidney which were causing considerable pain were removed by

TABLE 1.—PRE-OPERATIVE AND POSTOPERATIVE DATA ON PATIENT 32.

Date.	Ca. mg.	P, mg.	Phosphatase, Bod. Units.	Protein, gm.	Serum per 100 cc.	
				
2/24	11.2	2.8
2/26	10.2	2.5	3.4	4.9
2/27	10.4	2.1
2/29	11.5	2.6
3/7	10.3	2.5
3/14	10.8	2.9
3/23
3/26	9.6	4.2
3/31	9.6	3.6

Parathyroid operation

Dr. George C. Smith on March 4, 1936. In Table 1 the important blood chemical data are recorded. Before operation the serum calcium values with possibly two exceptions were within normal limits; the serum inorganic phosphorus level was persistently low; the serum phosphatase was normal (cf. no bone disease). A normal serum calcium value coupled with a low phosphorus value is very suggestive of hyperparathyroidism in a person with a low serum protein. The latter determination was accordingly done and found low. If one corrects the serum calcium values on March 7th and March 14th, when the serum protein values were 4.9 and 5.2 gm. respectively, for what they would have been at a serum protein value of 6.5 gm. one obtains, instead of 10.3 and 10.8 mg., 11.9 and 12.0 mg.* The corrected values were highly suggestive of hyperparathyroidism. In addition, the patient excreted 263 and 222 mg. of calcium per 24-hour period while on a low-calcium diet, normal being about 65 mg. The stones were largely calcium phosphate; there was no other cause for the stones found—no obstruction—no infection. A diagnosis of mild hyperparathyroidism was made. On March 23, 1936, Dr. Edward D. Churchill removed a small adenoma of the left lower parathyroid (1.1 by 0.6 by 0.3 cm.) (v. Fig. 5). This patient is an excellent example of the importance of the serum protein determination; she illustrates, furthermore, the value of urinary calcium determinations for confirmatory evidence.

Patient 18, Janilly F. (Al. G. H., No. 336257, previously published), a married woman, aged 58, was sent to this hospital by Dr. H. Goodale, of

* To obtain the "corrected serum calcium" value one may use the following equation, which was derived from the basic equation of McLean and Hastings¹¹ for the ionization of calcium protinate.

$$(1) \quad [\text{Total Ca}] = \frac{[\text{Ca}^{++}] \times ([\text{Ca}^{++}] + [\text{total prot}] + K)}{K + [\text{Ca}^{++}]}$$

However, before this may be done, the calcium ions in the given serum of lowered serum protein content must be calculated from the following equation of McLean and Hastings¹¹

$$(2) \quad [\text{Ca}^{++}] = \frac{[\text{total Ca}] - [\text{total prot}] - K + \sqrt{4K[\text{total Ca}] + ([\text{total prot}] - [\text{total Ca}] + K)^2}}{2}$$

Ca⁺⁺, total Ca, and total prot represent millimoles per kilo of water and K = 10⁻² in both equations. Water (in gm. per 100 cc.) = 99.0 ~ 0.75 P (P = gm. of protein per 100 cc.). Total protein in millimoles may be obtained by multiplying protein in gm. per liter of water by the Van Slyke, Hastings, Miller and Sandoz¹² factor 0.25¹³ assuming a pH of 7.35 and an albumin to globulin ratio of 1.5. A correction for the decreased water content (*vide supra*) of the serum with the normal serum protein content will have to be applied to the total Ca of equation (1) to obtain the total Ca in the serum of normal protein content. It is to be noted that the square in the term ([total prot] - K)² was left off in the original article as a result of a misprint.

Worcester, because the clinical picture appeared to be that of hyperparathyroidism, although the blood chemistry did not seem to confirm the diagnosis. Ten years before admission she had slipped on a wet floor and had fractured her left femur. Ever since then she had had a residual lameness requiring crutches. Nine months before admission she had fainted on a hot day and had again fractured her femur and in addition her left humerus. The hip fracture had not united. There had been no symptoms referable to the urinary tract, but she had lost considerable weight (over 50 lbs.) and strength during the past 10 years. Her diet had not been inadequate. She had lost perceptibly in height. The interesting points on physical examination were adentia, a palpable nodule in the thyroid region (later demonstrated as a thyroid nodule), a moderate hypertension, a thoracic kyphosis, and the changes in her left leg. Roentgenograms showed generalized decalcification, cyst formation, and the ununited fracture of the middle third of the left femur. There was no evidence of kidney disease.

The calcium and phosphorus values before operation were suggestive of a mild hyperparathyroidism. (Table 2.) There were two surprises. It was

TABLE 2.—PRE-OPERATIVE AND POSTOPERATIVE DATA ON PATIENT 18.
Serum per 100 cc.

Date (1934)	Ca, mg.	P, mg.	Phosphatase Bod. Units.
4/4	11.4	2.5	
4/10	11.7	2.8	5.7
4/13	Parathyroid operation		
4/17	9.8	3.5	
4/23	9.3	3.3	4.8
4/25	9.7	3.3	
(1935)			
5/16	9.9	2.1	7.5

unusual that a person with so little hyperparathyroidism should develop so much bone disease; furthermore, with the presence of marked bone disease why was the phosphatase level not definitely elevated? The prediction was made that the patient would have a very small tumor and that a bone biopsy would show mostly osteoporosis with relatively little bone destruction and bone formation. The reasoning was as follows. The amount of bone present depends on the balance between bone destruction and bone repair. In senile osteoporosis, the primary trouble is with bone repair. In hyperparathyroidism with bone disease, the primary trouble is increased bone destruction which is partly met by increased bone repair. If the two diseases should coincide, a mild degree of hyperparathyroidism might lead to a small amount of bone absorption, which, if not offset by an equal amount of bone repair because of an associated senile osteoporosis, would result in a marked decrease of bone tissue. In such a situation the serum phosphatase level being an index of the amount of bone repair would not be elevated and would form an exception to the general law that the phosphatase level is an index to the amount of bone disease.

The patient was operated upon by Dr. E. D. Churchill and a parathyroid adenoma 1.2 by 0.8 by 0.4 cm. was removed. A semilunar area of normal parathyroid tissue was present at one end. The tibial biopsy confirmed the pre-operative hypothesis (v. Fig. 6). The patient showed marked improvement during the next year; she gained 25 pounds; roentgenograms showed increased density of bones. The ununited fracture because of bad position remained ununited. The patient refused an open reduction.

Patient 31, Esther S. (M. G. H., No. 346778), a married woman, aged 34, was admitted to the Urological Service in July, 1935, because of pain in the right flank. Bilateral renal calculi were found; two stones were removed from the right ureter and patient was discharged.

TABLE 3.—PRE-OPERATIVE AND POSTOPERATIVE DATA ON PATIENT 31.

Date	Ca.	P.	Phosphatase.
(1935)	mg.	mg.	Bod. Units.
7/15	13.1	2.4	
7/17	10.4	2.7	
7/20	10.4	2.7	
7/25	11.4	3.4	
10/10	11.5	2.8	
(1936)			
1/1	11.1	2.7	
1/9	11.1	2.7	
1/13	11.2	2.9	
1/22	11.2	2.9	
1/27	9.4	4.2	Parathyroid operation

4.7

3.7

In Table 3 the pre-operative and postoperative chemical data are shown. The first determination was almost diagnostic of hyperparathyroidism, provided it could be checked. However, it could not be. The serum inorganic phosphorus figures were with one exception consistently low. Unfortunately the serum protein was not determined. The serum phosphatase was normal, which agreed with the fact that there was no bone disease demonstrable by roentgenogram. The calcium excretion in the urine by rough tests seemed increased. The stones were largely composed of calcium phosphate. On January 23, 1936, Dr. Oliver Cope removed a parathyroid adenoma 1.5 by 1.0 by 0.4 cm., weighing 0.45 gm. This tumor again was so small that a rim of normal parathyroid tissue extended more than half around the tumor (v. Fig. 7). This patient illustrates very well the importance of doing repeated blood determinations. Thus if the first determination had been that of July 25 it is probable that the diagnosis would not have been made until the patient returned to have more stones removed. Patient 33, Mary McD. (M. C. H., No. 320925), first entered the Urological Service in April, 1932, for a questionable renal tuberculosis and was discharged with the diagnosis of pyelonephritis. She complained at that time of pain in the kidney region and showed pyuria and albuminuria. Urine culture showed a B. coli infection. Roentgenographic studies of the kidneys showed calcium deposits in the region of the pyramids (Fig. 8). This unusual roentgenogram later was brought to the attention of one of us (F. A) and it was realized that calcium deposits in the collecting tubules is very suggestive of hyperparathyroidism with Type II renal lesions.² Accordingly, the patient was asked to return for blood chemical studies. It was then noted that her urine contained in addition to the pus many calcium phosphate casts showing that the Type II renal lesions were still being added to.

TABLE 4.—PRE-OPERATIVE AND POSTOPERATIVE DATA ON PATIENT 33.

Date	Ca.	P.	Phosphatase.	Protein.
(1935)	mg.	mg.	Bod. Units.	gm.
6/29	11.5	3.1		
7/6	12.2	3.5		
11/5	10.9	3.6		
11/9	10.5	3.0		
11/19	10.5	3.0		
(1936)				
3/31	10.7	3.7		
4/2	10.2	3.8		
4/4	10.6	3.8		
4/7	11.2	3.8		
4/18	11.2	3.8		

Parathyroid operation

4.2

8.2

11.1

6.1

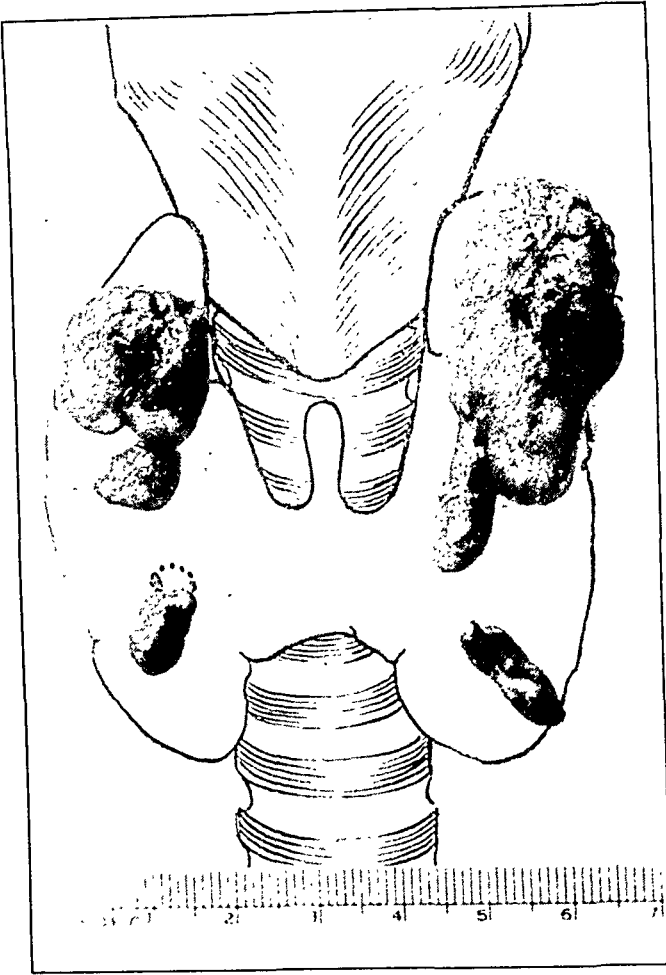


FIG. 1.—Photograph of parathyroid tissue removed at operation on Patient 25. Area enclosed by dotted line adjacent to right lower parathyroid gland represents amount of tissue left in place.

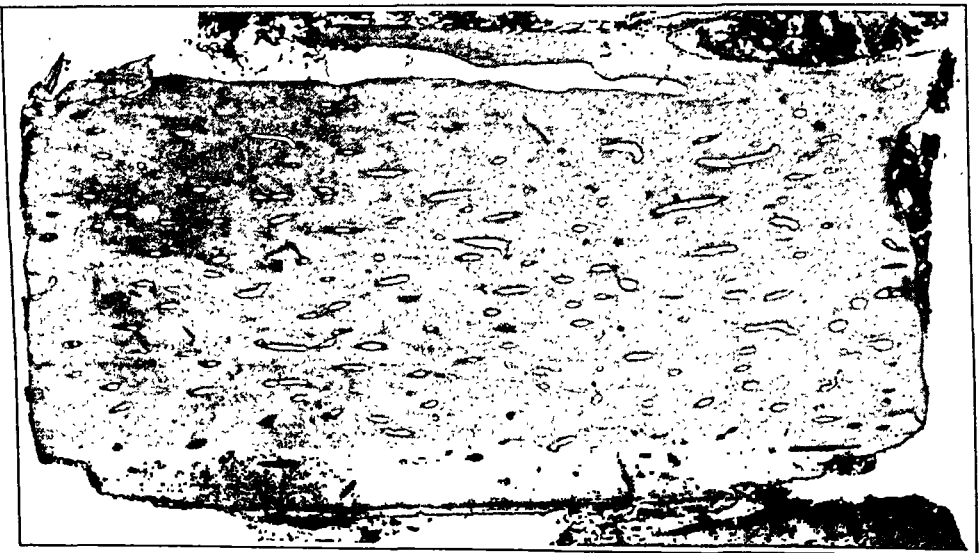
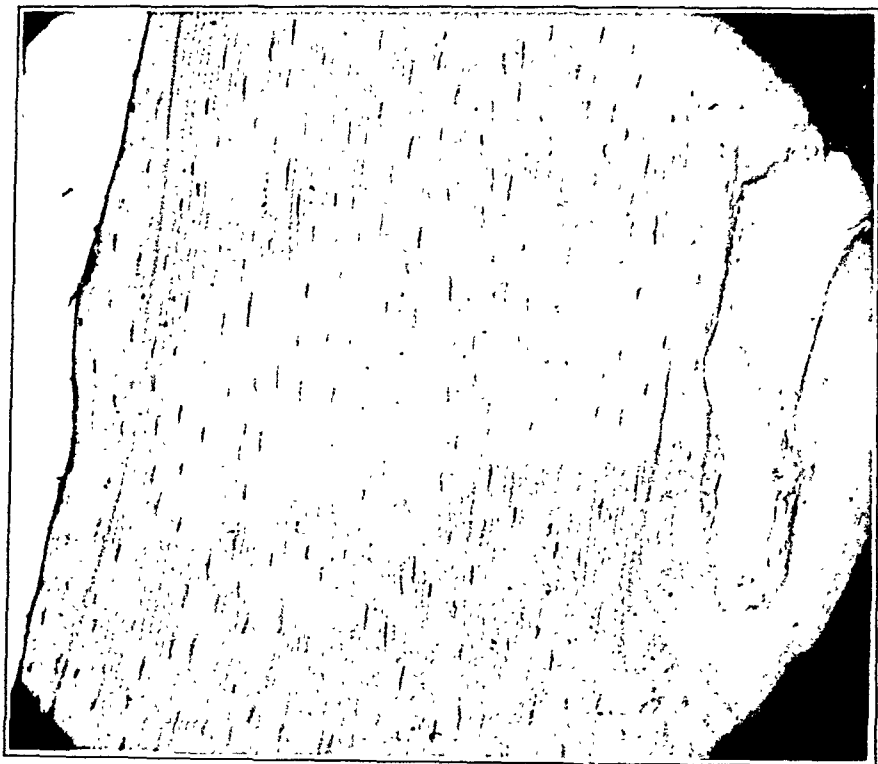


FIG. 2.—Low-power photomicrograph of tibial biopsy on Patient 25 performed at time of parathyroid operation. Note solidity of bone.

Fig. 1.—High-power photomicrograph of tibial biopsy on patient with hyperparathyroidism and bone disease for comparison with Fig. 3. Note marked bone destruction (osteoclasts ++), marked bone formation (osteoblasts ++), and fibrosis.



Fig. 3.—High-power photomicrograph of same specimen shown in Fig. 2. Note absence of bone formation, bone destruction, and fibrosis (cf. Fig. 1).



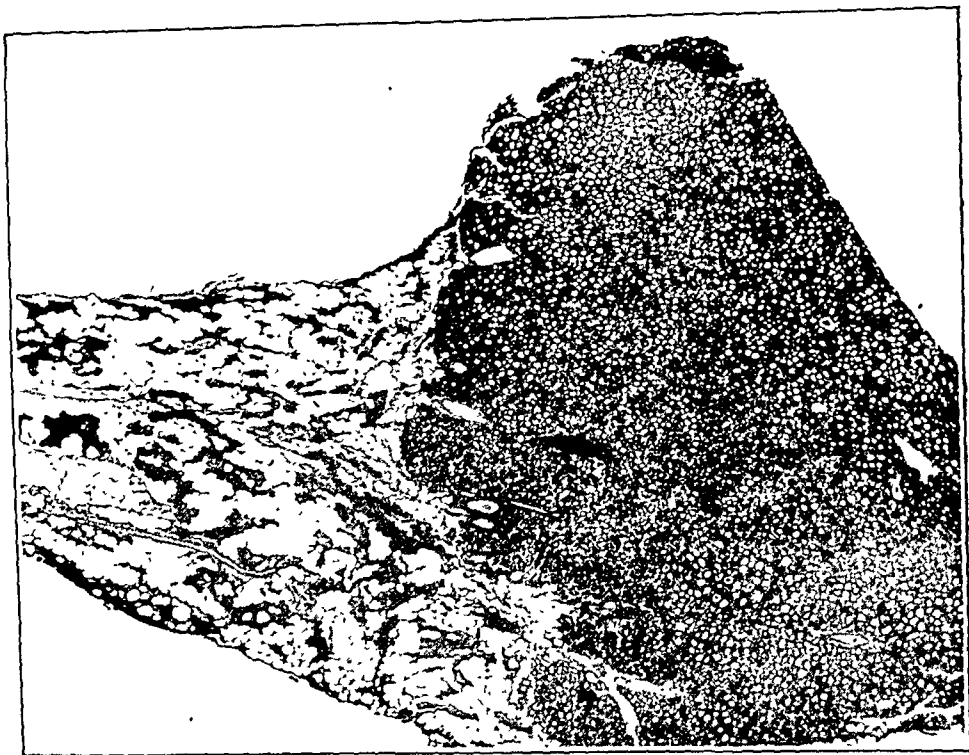


FIG. 5.—Photomicrograph of parathyroid tumor on Patient 32. Note that a large pedicle of normal parathyroid tissue is still intact. Note colloid in tumor, which might suggest thyroid tissue to inexperienced pathologist. Tumor and remainder of gland weighed 0.18 gm. Tumor measured 1.1 by 0.6 by 0.3 cm.; remainder of gland measured 0.7 by 0.3 cm.



FIG. 6.—Photomicrograph of sternal biopsy on Patient 18. Note absence of any marked evidence of bone destruction or of bone regeneration (*cf.* Fig. 4). See text for discussion.

Fig. 8. — Intravenous pyelogram on Patient 31. Note calcium deposits in pyramids of kidneys, a finding very suggestive of hyperparathyroidism.

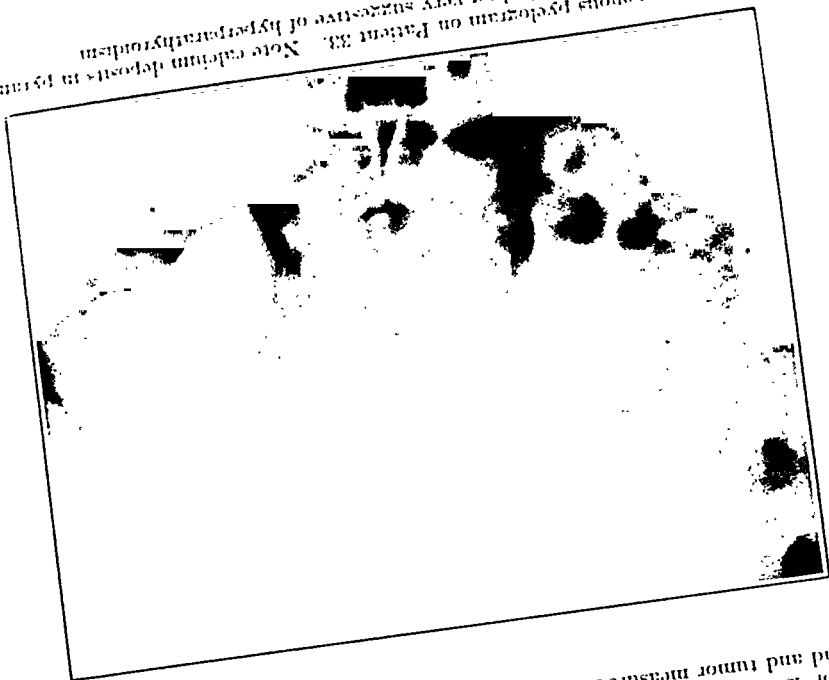
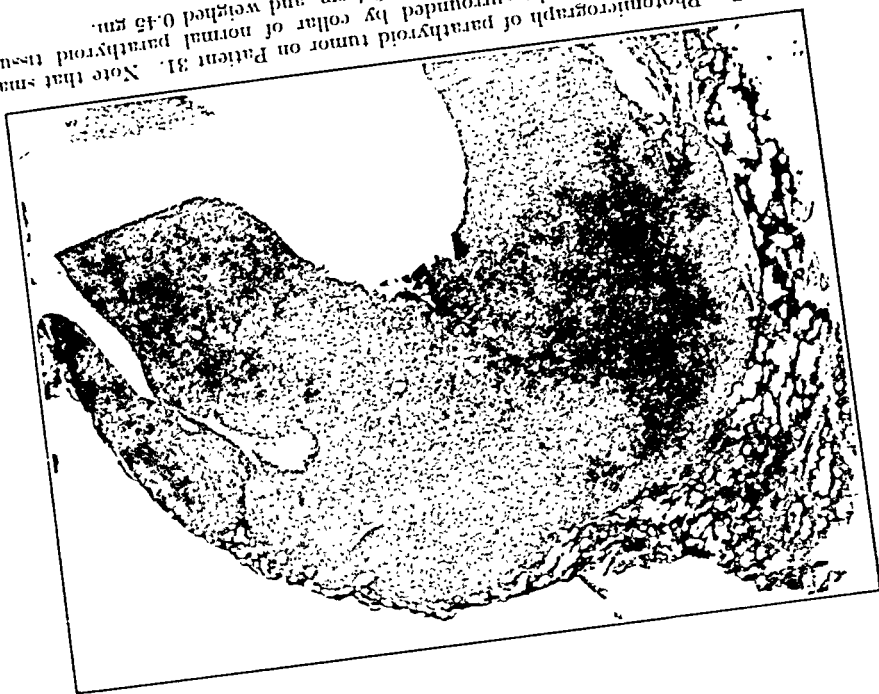


Fig. 7. — Photomicrograph of parathyroid tumor on Patient 31. Note that small tumor is almost completely surrounded by collar of normal parathyroid tissue. Gland and tumor measured 1.5 by 1.0 by 0.4 cm. and weighed 0.45 gm.



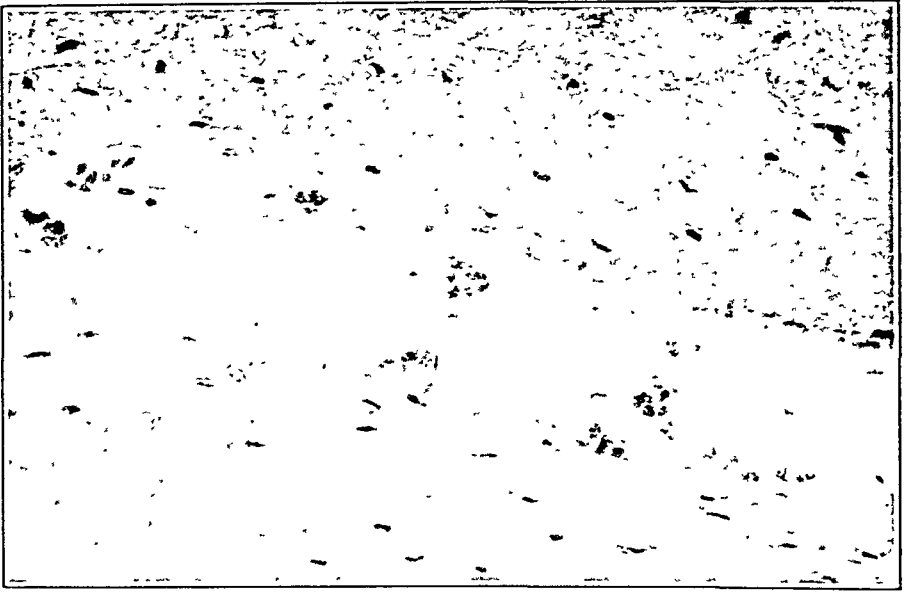


FIG. 9.—Photomicrograph of tibial biopsy taken at time of parathyroid operation on Patient 33. Note nest of osteoclasts, showing that, in spite of mild degree of hyperparathyroidism, bone resorption was occurring.

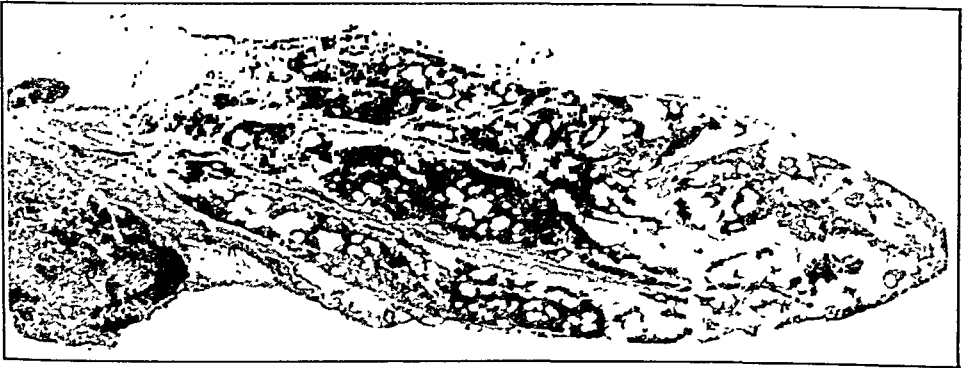


FIG. 10.—Photomicrograph of parathyroid tumor in lower pole of otherwise normal gland. Tumor was found at autopsy on a patient who had had renal calculi (see text).



In Table 4 her pre-operative and postoperative chemical data are shown. The pre-operative data were certainly not very convincing of hyperparathyroidism, especially the blood taken on March 31, 1936. The phosphatase was slightly elevated and she did show evidence of bone disease by roentgen-ray with generalized decalcification and a wedge-shaped fifth lumbar vertebra. It seemed important to study her calcium and phosphorus excretions. On a neutral-ash low-calcium diet she excreted in her urine per 3-day period 537 mg., 523 mg., and 614 mg. (the average normal value being 190 mg.⁷).

On April 2, 1936, Dr. Oliver Cope removed a parathyroid tumor measuring 0.8 by 0.6 by 0.3 cm., and weighing 0.16 gm. The casts immediately disappeared from her urine.*

This patient was selected for special consideration partly because she had a mild hyperparathyroidism in spite of almost normal blood values, but mostly because she was developing a serious kidney situation in spite of her very mild degree of hyperparathyroidism, as well as definite bone changes (Fig. 9). Why she should develop this type of kidney lesion and another patient should develop stones in the kidney pelvis is not known. The diagnosis in this case depended on the clinical picture and the hypercalcinuria.

In the series of 35 cases there were 8, including the 4 cited, which are being classified as borderline cases. In most of these the tumor was so small that it had not entirely destroyed the parathyroid gland in which it was situated. The cases, it is believed, were milder as regards the degree of hyperparathyroidism than any other single proved case yet reported from other clinics, and, therefore, it is argued, they presumably would not have been picked up in most other clinics. All but 2 of these cases fall into previous groups. Subtracting these 2 cases from the 6 there remain only 4 cases unaccounted for.

This is not all. Of the remaining 4 cases, 2 were extremely unusual and cannot be grouped with other cases. One was the girl aged 13 with marked renal insufficiency reported by Albright, Baird, Cope and Bloomberg,³ a case which remains unique, and in the other patient the diagnosis was arrived at almost by accident and was the subject of a separate communication by Albright.¹⁶

There remain, therefore, out of 35 cases only 2 which were not sent to this hospital and were not entirely different in character from cases diagnosed elsewhere. A series of 2 cases about corresponds with that of other clinics of similar magnitude. The corollary to the discussion is that if lack of ultraviolet radiation has caused the large series here, there remains to be explained why the type of case also varies so widely from that found elsewhere. Of the 13 cases sent to this hospital on the other hand, 9 were the classical type, 3 were the cases without bone disease discussed above, and the remaining 1 was Case 18, abstracted above.

Additional Discussion. In Chart II some further interesting

* This patient's urinary calcium excretions on a neutral-ash low-calcium diet, per 3-day period, during February, 1937, were: 304 mg., 373 mg., 578 mg. The third of these values is still distinctly high, but the first two were sufficiently within normal limits to rule out hyperparathyroidism.

points are brought out related to the presence or absence of bone disease. As pointed out in a previous paper, a high serum phosphate level is indicative of marked bone disease, in that this value is proportional to the amount of bone repair. This law of course holds only when bone repair is proportional to the amount of bone destruction present. Thus in Case 18, which is construed as having had a fundamental disturbance in bone repair (*i. e.*, senile osteoporosis) coupled with a mild hyperparathyroidism, there was marked bone disease without an elevation of serum phosphatase. In Chart II, the serum calcium values of patients with high serum phosphatase levels have been connected with broken lines rather than full lines. Two things are apparent. The patients with bone disease (high phosphatase levels) were not necessarily the ones with the severest degree of hyperparathyroidism, but are distributed along at all levels. Following operation this group of patients developed marked hypocalcemia. This chart shows why it has been repeatedly emphasized that patients with high phosphatase levels should be handled very conservatively regarding the removal of parathyroid tissue. In fact, in most cases they should have their tumors resected rather than entirely removed at the first operation. From the discussion above it is apparent that the diagnosis of hyperparathyroidism has been made with quite slight chemical changes from the normal. It would be misleading not to point out that there have been 3 patients indistinguishable from the borderline cases discussed above in which exploration was performed without the finding of a parathyroid tumor. Such a case was the following.

Patient, Albert H. (Al. G. H., No. 352487), a 41-year-old chauffeur passed his first urinary calculus 18 years before entry and a second stone 2 years before entry. He passed smaller stones subsequently. On March 17, 1936, a stone was removed from the left ureter by Dr. Richard Chute. Chemical analysis of his stone showed it to be largely calcium phosphate. The chemical data on his serum were as follows:

Date.	Calcium, mg.	Phosphorus, mg.	Protein, gm.	Phosphatase
3/29/35	11.5	2.3	2.8	2.9 Bod. U.
4/1/35	10.7	2.8	2.8	5.4
3/26/36	9.7	2.8	2.8	...
4/11/36	10.8	2.8	2.8	...

The patient was put on a neutral-ash low-calcium diet and excreted in his urine per 3-day period S38 and S39 mg. of calcium (normal being about 190 mg.). There was no bone disease demonstrable by Roentgen-ray (*cf.* normal serum phosphatase level). A parathyroid exploration was performed by Dr. Oliver Cope on April 13, 1936. Three normal appearing parathyroid glands were found; the fourth was not demonstrated; no tumor was found. And yet this patient had a very high urinary calcium excretion, a persistently low serum inorganic phosphorus level, a serum calcium value on the high side (especially when allowance is made for the low serum protein), and the right kind of stones.

The question arises whether these patients with negative explorations represent faulty diagnoses or whether tumors were present and not found. This question cannot be answered. In no one of these particular 3 cases, were all 4 parathyroid glands found. Even if they had been, the possibility exists that the tumor might have been so small that it was mistaken for a normal gland, or was entirely embedded in a normal gland. Such a possibility seems fantastical but the following case brought to our attention by Dr. Benjamin Castleman at least suggests the possibility.

Patient, Alice S. (M. G. H., No. 328221), entered the Urological Service in April, 1933, at the age of 30. She had been in good health until $6\frac{1}{2}$ years before admission when she had begun to pass gravel. A suprapubic cystotomy had been done in 1927 with the removal of stones. A urinary fistula had persisted ever since. She had a badly infected urine and a high non-protein nitrogen level in the blood. A bilateral nephrostomy was performed, but she died on her 25th postoperative day. No calcium and phosphorus studies were performed.

Autopsy revealed a "bilateral pyohydronephrosis." There was a minute parathyroid adenoma in one of the glands (Fig. 10).

The question is, of course, whether this minute tumor caused hyperparathyroidism, renal calculi, and death. If it did, it is obvious that tumors as small as this could not be recognized with the naked eye and might be entirely surrounded by normal parathyroid tissue. It is an interesting and important question.*

Summary and Conclusions. 1. This paper is based on 35 cases of hyperparathyroidism proved by operation studied at this hospital. It represents a 10-year experience.

2. This series comprises 13 cases sent to the clinic already suspected of having the disease and 22 cases first diagnosed here. All but 2 of the 22 cases had clinical findings entirely different from cases being reported in the literature from outside clinics. The conclusion is made that the series is so large because cases are being recognized which are being missed by other clinics.

3. There are two groups of cases in particular which have accounted for multiple cases at this hospital and which are not being recognized elsewhere. These are:

a, Cases with no demonstrable bone disease—12 cases.

b, Cases with a very moderate degree of hyperparathyroidism—8 cases.

4. The presence or absence of bone disease is not a function of the degree of hyperparathyroidism, some of the severe cases not having

* Dr. Bruce Chown, of The Children's Hospital of Winnipeg, Canada, communicated with Dr. Benjamin Castleman about a somewhat similar case. A woman aged 46, who died of rupture of an aneurysm of the circle of Willis, had at autopsy a minute adenoma composed of oxyphil cells in one of the parathyroid glands. She had had a nephrectomy for stone in 1928. The remaining kidney at autopsy was somewhat enlarged and microscopically showed small areas of chronic nephritis and minute calcium deposits. Dr. Chown expects to publish this case in detail, but has kindly consented to our mentioning it.

it, some of the mild ones having it. Patients with bone disease and high serum phosphatase levels as a rule develop postoperative hypocalcemia; other cases seldom do.

5. The term "border-line" has been applied to mild cases of hyperparathyroidism and refers to the degree of hyperparathyroidism, not to the symptoms. In the diagnosis of such cases the following points may be important:

a, The serum protein determination, so that allowance can be made for the "bound" calcium in interpreting the total calcium value;

b, A persistently low serum phosphorus level.

c, The calcium excretion in the urine.

d, The composition of the stone.

e, Repeated blood determinations.

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ADRENAL CORTICAL ADENOMA WITH ABSENCE OF THE OPPOSITE ADRENAL.

REPORT OF A CASE WITH OPERATION AND AUTOPSY.

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It is now generally recognized that many of all of the features of Cushing's syndrome may be associated with a variety of endocrine tumors. Basophilic adenomas of the pituitary, adrenal cortical tumors, arthenoblastomas and thymic carcinomas have all been

described as causes of the clinical picture related to the pituitary by Cushing.³ The following case displayed almost every feature of Cushing's syndrome and is presented because the problems of diagnosis and treatment can be related to the pathologic findings.

Case Report. The past medical history was not significant.

Present Illness. Began in 1932 at the age of 25 to gain rapidly in weight (20 pounds) and had pain in the legs. Shortly after she noted loss of hair on the scalp, increased appetite, thirst, polyuria and increased huskiness of her voice. The menses, which had begun at 12 years and been normal and regular, became scanty and irregular in 1933, when she also noted purple striations on her abdomen, a bluish discoloration of her feet and excessive growth of hair on her face, back and arms. She also noticed frequent ecchymoses over the dependent portions of her body. Complete amenorrhea developed in April, 1935, at which time she experienced a dull persistent pain over the right lumbar region. She believed that she had become shorter in stature during the past several years.

Physical Examination. She was a somewhat sluggish, young, white woman of plethoric appearance, with marked abdominal obesity, her height being 56 inches and her weight 150 pounds. Her face was very round and full, causing the eyes to appear slightly shut. The obesity was limited to the face, thorax and abdomen (Fig. 1). Over the breasts, axillæ and abdomen there were many prominent purple striations and the lower legs were cyanotic. The skin was dry, coarse and inelastic. Over the cheeks, upper lip, chin and back there was an excessive growth of hair. The hair on the back was perhaps the most strikingly masculine of all these regions. There was partial baldness of the scalp. The eyes were normal except for a small hemorrhage in the fundus of the right eye; the disks were normal. The thyroid was not palpable. The lungs were negative. The heart was slightly enlarged to the left with an accentuated aortic second sound. The blood pressure was 210/140; pulse, 80. Abdominal palpation revealed no masses or tenderness. On pelvic examination the clitoris was normal, while the uterus was only about half normal size.

Laboratory Studies. On admission the blood count was as follows: erythrocytes, 5,300,000; hemoglobin, 102% (Sahli); leukocytes, 11,000; neutrophils, 67%; lymphocytes, 23%; monocytes, 10%. The reticulocytes were 2.1% and the platelets 448,000. The coagulation and bleeding times were normal. Urinalysis: the specific gravity ranged from 1.010 to 1.025; moderate albumin, no sugar. There was an occasional hyaline and granular cast.

Blood Chemistry. Blood urea nitrogen was 13, the fasting blood sugar 113 mg. per 100 cc. Although the urine was consistently sugar-free on the ward diet, she had a diabetic sugar-tolerance curve as follows:

	Blood sugar.	Urine sugar.
Fasting	113	0
$\frac{1}{2}$ hour after 100 gm. glucose	240	+
1 hour after 100 gm. glucose	330	++++
2 hours after 100 gm. glucose	320	++++
3 hours after 100 gm. glucose	242	++++
4 hours after 100 gm. glucose	185	++

The blood cholesterol was 390 mg. per 100 cc.; serum calcium, 10.4 mg. per 100 cc.; serum phosphorus, 3.4 mg. per 100 cc.; blood phosphatase, 32 units. Phenolphthalein test of kidney function showed 65% in 2 hours. The basal metabolic rate was +2%.

The electrocardiograph showed simple tachycardia and left-axis deviation. Orthodiagram showed the heart to be enlarged 17% above the predicted normal area.

The visual fields were normal. Roentgen ray films of the pituitary fossa showed apparently normal measurements (8.5 by 6.5 cm.) but examination was considered not entirely accurate because of the degree of decalcification of the posterior clinoid process. This decalcification was also manifested in the bones of the calvarium, feet, pelvis and lower spine. Very marked arteriosclerosis was demonstrated by Roentgen ray, in the arteries of the legs. There were multiple fractures of the ribs, although no history of trauma was obtained. Gastro-intestinal Roentgen ray showed a distinctly abnormal small intestinal pattern characterized by an increase of tone and peristaltic rushes. A urogram revealed a normally functioning urinary tract in which there were no shadows or distortion of the kidney outline that suggested adrenal tumor.

The tentative diagnosis was Cushing's syndrome due to basophilic adenoma of the pituitary or to an adrenal cortical tumor. The outstanding features therefore were the onset of abdominal obesity in 1932 at the age of 25, followed by the progressive development of hirsutism, amenorrhea and masculinization and diminished glucose tolerance were observed. There were no neurologic or routine Roentgen ray findings which served to differentiate the possible pituitary or adrenal tumor that was suspected. Subsequent Course. On February 27, 1936, Roentgen ray therapy of the pituitary gland was instituted. Treatment, continued until March 15, 1936, gave a total dosage of 1000 r. She had one abortive menstruation at the time of the first treatment. Except for this there was no change whatever in her condition, and on April 21, 1936, she was transferred to the Surgical Service of Dr. E. L. Eliason. On April 22, 250 cc. of air were injected into the retroperitoneal spaces followed by Roentgen ray examination, according to the method of Cahill *et al.* This revealed a possible adrenal tumor on the right side (Fig. 2).

Operation. April 27, 1936. The abdomen was explored through a right subcostal incision (Cahill *et al.*). The left adrenal was not seen or felt, but the peritoneum on this side was not opened for exploration of the subperitoneal fat. After opening the posterior peritoneum on the right, the right adrenal was exposed. The residual emphysema from the air injection was an added source of difficulty at this stage. The right adrenal was found to contain a well-encapsulated mass measuring 3.5 by 3 by 3 cm. This was removed, leaving part of the right adrenal *in situ*. The usual postoperative measures including fluids, glucose and saline were employed. After operation the patient developed a sustained fever of 102° to 104° F. which persisted until her death on the eighth day. With this elevation of temperature no sweating was noticed, although she perspired freely on returning from the operating room. In spite of this severe reaction she was comfortable and clear mentally, giving one a false impression as to her well-being. She was able to eat an adequate soft diet during this time. Because of her fever no metabolic studies were attempted, but her blood pressure showed a striking change. The most striking physiologic response to the removal of the tumor was the prompt fall of the blood pressure to a normal level. This was constant and sustained for 6 days, until the pre-mortem fall to the shock level occurred. This and the other findings during this period are summarized in Fig. 3. She went into shock and died on the eighth day after operation. The terminal serum chloride was 88 m Eq/L. and the serum sodium 127 m Eq/L. Autopsy. (Dr. O. Norris Smith; 4½ hours after death.) There was

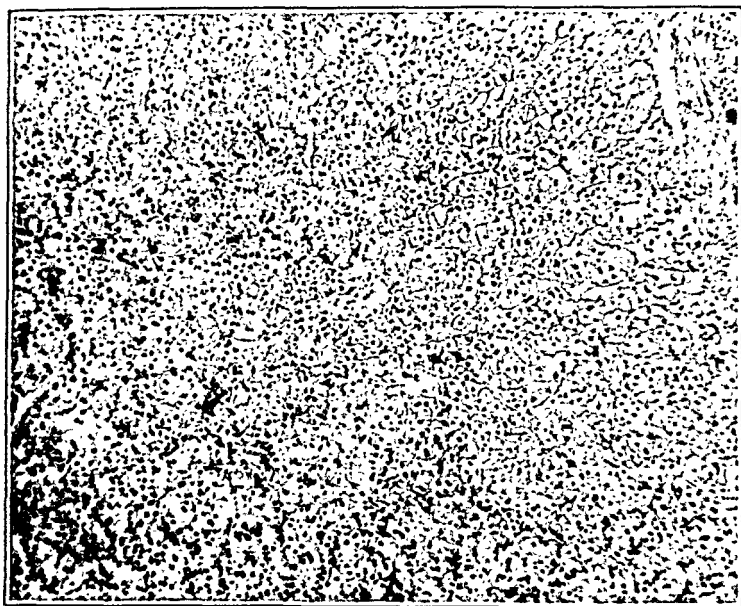


FIG. 1.—Abdominal striae and general configuration.



FIG. 2.—Roentgen ray of adrenal regions after air injection.

Fig. 4.—Adrenal cortical tumor ($\times 92$).



massive adipose deposition in the viscera. The operative site and neighboring structures showed no signs of infection or hemorrhage, the only changes being the expected minor exudative reaction.

The *lungs* showed moderate bilateral atelectasis, due to the elevated diaphragm. The *heart* (380 gm.) was of normal size, but showed moderate left ventricular hypertrophy. The coronaries and endocardium showed slight atherosclerosis with no occlusion. The aorta was the site of diffuse, marked atherosclerosis without calcification or ulceration. The bones were thin, and easily broken or cut, suggesting diffuse osteoporosis. The *liver* (1860 gm.) was enlarged, soft and yellow in color. The extreme fatty change was determined chemically, the fatty acids being 35 gm. % (normal, 2 to 5%). The *spleen* (130 gm.) was slightly congested. The *pan-*

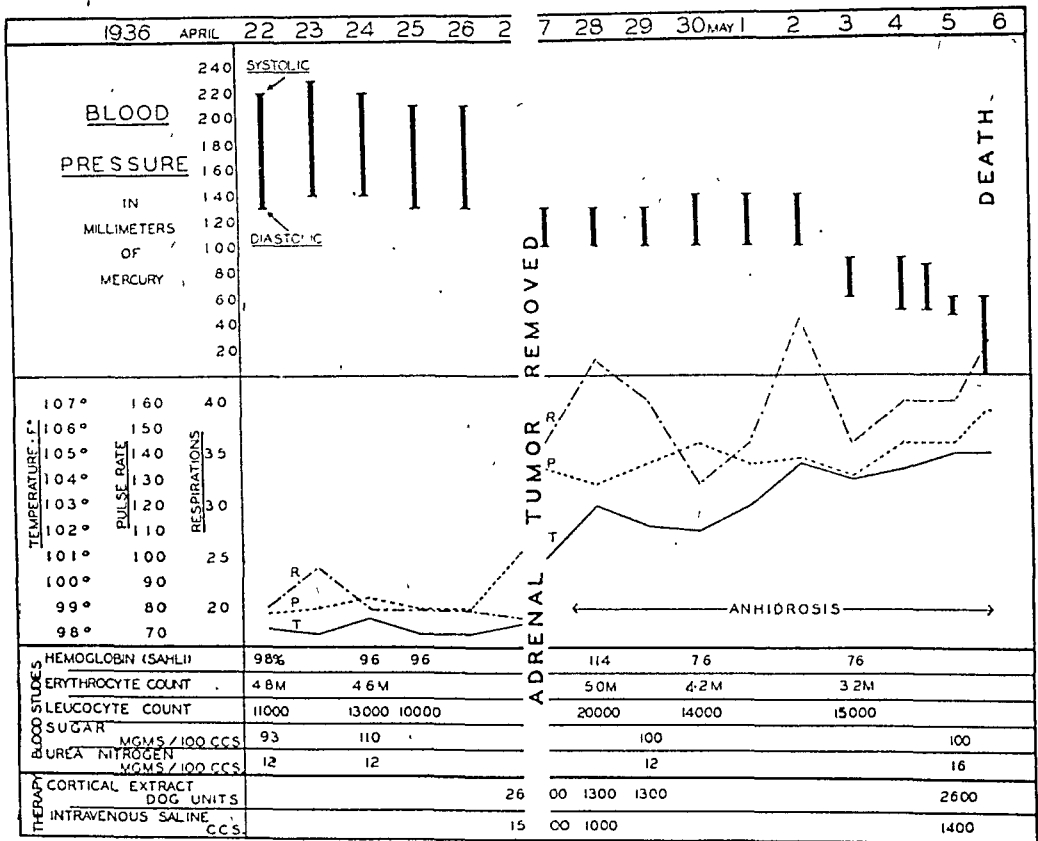


FIG. 3.—Summary of postoperative course and findings.

creas appeared normal in size but was distinctly more firm than normal. The *kidneys* showed an infiltration with yellow deposits similar to the liver and they were slightly granular. The *gastro-intestinal tract* was grossly normal.

Histologic Study. This showed in the *heart* intimal thickening without occlusion of the coronaries and hypertrophy of the muscle fibers. There was marked patchy atheromatous degeneration of the *aorta*. The *lungs* showed slight congestion and edema and a mild bronchiolitis in the left lobe. In the *liver* no normal cells were seen, the tissue consisting chiefly of large "seal ring" cells with moderate vascular engorgement. The arterioles of the *spleen* were thickened. In the *kidney* there was lipoid nephrosis and mild benign nephrosclerosis. The *bones* showed definite osteomalacia. Section of the *skin* revealed no localized lesion that accounted

for the striae, although there was slight segmented thinning and atrophy of the corium.

Adrenals. The left adrenal could not be found despite careful dissection of the entire perirenal fatty tissue on that side. The remaining part of the right adrenal was grossly normal in structure but much smaller than usual. The upper portion containing the bed of the tumor which was filled with a small, clean clot. Microscopically, this adrenal cortex was rather pale, the zona reticularis being especially washed out. The medulla was prominent in one section, not discernible in others, and was probably not abnormal. The portions of the gland next to the bed of the encapsulated tumor showed hemorrhage and necrosis. The gland was not weighed but was estimated to represent approximately half of a normal adrenal in size. **The Adrenal Tumor.** Section showed a very cellular tumor that was well encapsulated (Fig. 4). There was very little stroma. The cells were of the cortical adrenal type. Their arrangement was orderly and similar to that seen in the zona fascicularis. The cells appeared to be mature and well-differentiated and contained abundant lipid material. The nuclei were uniform in size and their relation to the cytoplasm was about the same in all cells.

In the *thyroid* region no tumor or mass was demonstrable. The tissue removed for section showed only adipose tissue, with no trace of thymus remnants. **The thyroid gland** was not enlarged. Microscopically, the thyroid tissue was pale, fairly cellular, the acini moderately filled with homogeneous colloid separated from the acinar epithelium often by large clear vacuoles. There was no clear evidence of involution or hyperplasia. Marked arteriosclerosis was noted in the thyroid.

No *parathyroid* tissue was found in the thyroid or the capsule. The tissue outside the capsule was not exhaustively examined. **Pancreas.** The predominant pathologic feature here was the extensive sclerosis of arteries and arterioles, many of the latter being plugged with dense fibrin. There was an extensive lobular fibrosis at places apparently completely destroying the acinar tissue but leaving clumps of islets, this process being more prominent in the head of the pancreas where the islets were very sparsely scattered. In the section from the tail of the pancreas fibrosis was minimal, while the islets were abnormally large, numerous and cellular.

The *uterus* was small (approximately 4 by 5 by 1.5 cm.). Histologic section showed an intact endometrium with short atrophic glands. The myometrium was extensively fibrotic. **The ovaries** each measured about 3 cm. in greatest diameter. Microscopically, the interstitial stroma was abundantly cellular, the serosa normal. There were extensive patches of scar tissue. No primary or developing follicles could be found. **The breasts**, while large from obesity, showed atrophy of the glandular elements histologically.

The pituitary (Dr. I. T. Zeekwer): The vessels of the brain were not markedly sclerosed. The pituitary was thought to be slightly enlarged in the lateral diameter. On careful review of serial sections no adenoma was found. The basophil cells seemed somewhat reduced in number. Some of the basophils contained intracellular hyaline material of the type described by Crooke as occurring constantly in cases of Cushing's syndrome. In one section a few basophils had infiltrated the posterior lobe. The acidophils were numerous.

Discussion. The patient described represents an instance of an adrenal cortical tumor associated with the fully developed picture

TABLE 1.—ORDER OF FREQUENCY OF PRINCIPAL SYMPTOMS OF 55 PROVED CASES OF TUMORS OR HYPERPLASIA OF THE ADRENAL CORTEX (1917-1935),
45 FEMALES, 10 MALES.

	Virilism or hirsutism.	Amenorrhea.	Obesity.	Hypertension (150 mm.).	Glycosuria.	Striae.	Decalcification.*	Increased M.B.A.*
Carcinoma or hypernephroma (30)	24	17	15	15	12	6	4	2
Adenomata (14)	12	8	6	7	5	5	3	1
Hyperplasia (11)	8	4	6	5	7	0	1	4
Total	44	29	27	27*	24	11	8*	7*
Per cent	80	65	49	49	44	20	15	13

* Not all cases examined for this abnormality.

of Cushing's syndrome. The incidence of the individual symptoms in 55 proved cases of adrenal tumor is summarized in Table 1. The unexplained elements in this case are especially the high post-operative fever without sweating for which no adequate cause can be assigned. It is possible that sweating was suppressed in an effort to conserve sodium chloride, but no such compensatory anhidrosis has been described in Addison's disease. The cause of death cannot be clearly stated. There was no evidence of infection or hemorrhage. Adrenal insufficiency is possible, but it is difficult to define the degree of this condition. In favor of adrenal insufficiency are: (a) The small and atrophic adrenal remaining on the right side; (b) the premortal fall in blood pressure; (c) the terminal blood chemistry. Questions arising in connection with this evidence are as follows: A. The amount of adrenal tissue remaining after operation would have supported an experimental animal. Thus, one-third of one adrenal maintains the appearance of health in the cat. B. The fall in blood pressure is compatible with any critical condition. C. The blood sodium and chloride were taken after salt administration and their original values may have been masked by this. However, the lowering of the sodium and chloride was not accompanied by the alterations in sugar and urea which might be expected on the eighth day of adrenal insufficiency. Furthermore, the extent of the electrolyte changes does not exceed that described by Sunderman, Austin and Camac¹¹ as occurring in pneumonia and other fevers. Whether this patient's high fever caused such changes or whether a tax upon adrenal function occurs in all fevers are points beyond speculation at present. Since there is no final answer to these questions, adrenal insufficiency is at least doubtful and the cause of death cannot be stated.

The absence of one adrenal has been reported by Miloslavich,⁹ Dietrich and Siegmund,⁴ and a few others, and once in a case of

cortical tumor by Reinblatt.⁹ Three additional cases of absence of one adrenal have been found in the autopsy records of this hospital since 1894. None of these were associated with contralateral tumor. A practical warning may be taken from the facts discussed. Before removal, inspect the side opposite the tumor. Following the removal of an adrenal cortical tumor, the blood should be carefully watched for the first signs of adrenal insufficiency. It may be that daily serum sodium determinations are necessary to do this, at least when the Cushing syndrome is present. The use of saline and cortical extract for 48 hours postoperatively is clearly indicated, as the majority of fatalities have occurred within that time. It is not possible to say how long such treatment should be continued, but the danger of adrenal insufficiency may not have passed in that short period. Of 40 cases of all tumor types operated upon, 19 died, although the recent mortality is less than this.

A few remarks may be made concerning the syndrome in general. The types of endocrine tumors causing all or part of this patient's picture have been described by others (Robb-Smith and Lescher¹⁰). The pathologic types of adrenal tumor have been reviewed.¹ The feature that has concerned us chiefly is the disturbance of carbohydrate metabolism. In this hospital it has been shown⁷ that removal of the adrenals modifies pancreatic diabetes in the cat. This alleviated diabetes is expressed by a markedly decreased glucose, nitrogen and acetone body excretion compared to that in the depancreatized cat, as well as by an increased period of survival. The carbohydrate tolerance of these animals is not significantly increased and the results appear due to a diminution of the production of glucose and acetone bodies rather than to their normal utilization. A similar modification of phloridzin diabetes in the rat after adrenalectomy has been demonstrated by Evans.⁵ It has also been shown¹¹ that adrenotropic extract of the anterior pituitary aggravates the diabetes to a very slight degree when the adrenals are absent and to a marked degree in the hypophysectomized-depancreatized cat in which adrenals are present. The details of the action of pituitary extracts are not yet fully understood.

The type of patient herein reported represents the opposite situation in which an excessive secretion of the adrenal cortex, hitherto impossible to produce experimentally, impairs carbohydrate metabolism. It is not known whether the adrenals exert this effect directly or through the pituitary or some other endocrine gland. The frequency with which adrenal cortical tumors cause glycosuria or impaired carbohydrate tolerance is shown in Table 2. In this connection the relationship of adrenal hyperplasia and glycosuria in 20 proved cases of pituitary basophilism is also summarized (Table 3). From Tables 2 and 3 it is apparent that the adrenal cortex may play an important part in carbohydrate metab-

olism. The relation of the adrenal cortex to carbohydrate regulation is not yet understood. However, experimental work^{3b} suggests that this is not regulated by the "salt-and-water" hormone but by some other element, which may be an unknown hormone of the

TABLE 2.—CARBOHYDRATE METABOLISM OF 55 CASES OF PROVED TUMORS OR HYPERPLASIA OF THE ADRENAL CORTEX (1917-1935).

	Carcinoma or hypernephroma.	Benign adenomata.	Bilateral hyperplasia.	Total.	Per cent.
Number of cases	30	14	11	55	100
No impairment of carbohydrate metabolism demonstrated . .	16	8	4	28	51
No fasting glycosuria, but impaired carbohydrate utilization after glucose	2	1	0	3	5
Glycosuria present:					
(a) Transitory	3	1	1	5	9
(b) Well marked	9	4	6	19	35
Cases with impaired tolerance	27	49

cortex or may be an expression of an interrelationship between the adrenal and the pituitary. The finding of the hyaline change of Crooke² in the pituitary in this patient suggests the latter mechanism.

Summary. A case of adrenal cortical adenoma is reported in

TABLE 3.—INCIDENCE OF GLYCOSURIA IN PROVED CASES OF PITUITARY BASOPHILISM.

Number of cases.	Glycosuria.		Adrenal cortex.		
	Present.	Absent.	Normal.	Hyperplasia.	Not noted.
20	14 (70%)	6	4	11	5 (all had glycosuria)

INCIDENCE OF GLYCOSURIA IN RELATION TO THE STATE OF THE ADRENAL CORTEX.

	Number of cases.	Glycosuria.	
		Present.	Absent.
Cortex hyperplastic	11	8 (73%)	3
Cortex normal	4	1 (25%)	3

CONDITION OF THE ISLANDS OF LANGERHANS IN THE CASES EXHIBITING GLYCOSURIA.

Number of cases.	Islands of Langerhans.		
	Normal.	"Fatty."	Not noted.
14	6	2	6

which the diagnosis was confirmed by operation and autopsy. The left adrenal was absent. The patient presented all the classical features of Cushing's syndrome. There was no pituitary tumor, but the basophil cells showed the hyaline change of Crooke.

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THE EFFECT OF SPLANCHNIC NERVE RESECTION ON PATIENTS SUFFERING FROM HYPERTENSION.

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INCREASED tone of the arteries in hypertension has been thought to be due, at least in part, either to increase in vasoconstrictor impulses acting on normal vessels or normal impulses acting on abnormally sensitive vessels. Since hypertension, similar to essential hypertension in man, has not been reproduced in animals, it has not been possible to test this hypothesis by experiment on them. The report of Craig and Brown¹¹ that resection of the splanchnic nerves caused arterial pressure to fall in patients suffering from essential hypertension, and that it did not appear to injure the patients, aroused our interest in the possibility of obtaining information on the participation of the sympathetic nervous system in the genesis and maintenance of elevated blood pressure.

The purpose of our investigation was to ascertain if possible the effect of splanchnic nerve resection and extirpation of the lower thoracic sympathetic ganglia on the immediate course of essential and malignant hypertension and on the special functions of the body, which one of us (I. H. P.) has been observing in connection with studies on the natural history of hypertension.

A considerable body of evidence, mostly physiologic in nature, indicates that the size of the vascular bed of the splanchnic region both in man and animals is important in the maintenance of arterial pressure (this evidence has been reviewed by Page and Heuer¹⁹³⁷).¹⁹

Most observers agree that the immediate cause of hypertension is narrowing of the peripheral arterioles.²⁰ (Observation of the

retinal arterioles and other vessels available for direct observation, such as those in the nail beds, lips, and conjunctiva, indicates that constriction is general. This has been further emphasized by the important experiments of Prinzmetal and Wilson⁴⁶ and Pickering.⁴⁴ They have shown that the blood flow in the forearm is the same in patients with hypertension as in normal persons. Were hypertension due to increased vascular resistance confined to some one area (splanchnic for example), the blood flow through the vessels in the rest of the body would be increased unless they too had contracted. If, on the other hand, the increased resistance is generalized and uniform, the blood flow in all parts of the systemic circulation will be the same as in normal persons—the high blood pressure simply overcoming the increased resistance in all areas. It is of interest to note, however, that the vascular lesions which are probably due to hypertension are usually limited to certain vascular areas. These lesions are notable in the kidneys, spleen and eyes, and we have repeatedly observed marked arteriosclerosis in the vessels in the meninges. These morbid vascular changes are almost wholly lacking in the great vascular bed of the muscles.^{3,20a,38}

Participation of the Nervous System in Genesis of Hypertension. Opinion differs on participation of the nervous system in the genesis of the hypertonus responsible for hypertension. The following observations favor the belief that the nervous system is involved. In many cases of hypertension marked nervous and mental instability is observed, especially early in the course of the disease.^{5, 13, 39b, 41, 47, 55a,b} The close association of this instability and the appearance of hypertension has been frequently and justifiably stressed. It is well known that emotion produces rise in arterial pressure. Stimulation of various regions of the hypothalamus and cerebral cortex produces marked rise in blood pressure.^{28, 31, 32, 51} Injuries to the nervous system may be associated with development of hypertension.⁶ Essential hypertension appears to be limited to man and chiefly to those men living under so-called "civilized conditions." In animals, hypertension that appears to be of nervous origin can be produced either by denervation of the carotid sinuses³⁴ or by injection of kaolin into the cisterna magna.¹⁶ Spinal anesthesia abolishes all vasoconstrictor impulses and consequently lowers blood pressure. The fall often is proportionately greater in patients with hypertension than in those with normal pressure.¹⁴ Section of anterior spinal nerve roots causes a sharp and prolonged fall in arterial pressure.² Injuries in which a transverse lesion of the cord has occurred in hypertensive patients have been followed by marked reduction in arterial pressure.

Vascular Hypertonus May Exist in the Absence of Central Nervous Connections. Evidence that vascular hypertonus in hypertension is due to an intrinsic property of the vessel wall is less extensive but nevertheless impressive. It consists of the observation that heat

applied to the body or anesthetization of the vasomotor nerves to the arm does not lead to a greater increase in the blood flow through the forearm in hypertensive than in normal subjects.^{44, 45} If greater increase in rate of blood flow should have occurred in hypertensive patients than in normal subjects. It may be objected that the viscera respond to removal of nervous control in a fashion different to that of the forearm. At least one important visceral organ behaves, however, somewhat similarly. It has been found that denervation of the kidneys does not appreciably increase urea clearance, and hence probably not the blood flow, in patients with essential hypertension.^{46a} The parallelism between urea clearance and renal blood flow was shown by Van Slyke, Rhoads, Hiller and Alving,⁵¹ in normal dogs. Had hypertension been due to impulses of central origin a marked rise in the rate of blood flow might have been anticipated. Page and Heuer¹⁰⁶ found no change in urea clearance or ability to concentrate urine, even after the extensive denervation of the kidneys produced by section of the anterior spinal nerve roots from the sixth thoracic to the second lumbar segments. Actual stripping of the renal pedicle of nerves in patients suffering from Bright's disease with hypertension was also without effect on the blood flow. It was concluded that the polyuria and increased activity of the denervated kidney observed in acute animal experiments did not occur in man.* This evidence appears to indicate that the hypertonus of the vessels of the kidneys, if such there be, is not primarily of nervous origin.

It seems impossible, on the basis of contemporary evidence, to decide whether hypertension of the vessels in hypertension is of nervous origin. Clinical evidence favors the belief that the nervous system actively participates, whereas evidence gathered by experimental methods favors the opposite belief. It does not appear improbable that the two views may be reconciled when knowledge of the mechanism of hypertension is more comprehensive.

Fall in arterial pressure is known to occur after severing the central connection of a portion of the sympathetic nervous system in patients suffering from hypertension. The phenomenon is consistent with either belief. In case the neurogenic view is urged, the fall in arterial pressure may be taken to depend upon prevention of *abnormal* tonic impulses from impinging upon *normal* vascular musculature; and when the vascular genesis is held, the fall may be

* The explanation for the discrepancy between these observations and the physiologic experiments on animals is probably to be found in the work of Kiliček, Pickford, Horthschild and Verney.⁴² They showed that the close parallelism in the rate of flow and in the compositions of the urine from the two kidneys of normal dogs remained unaffected by ligaturing a thread around the splanchnic nerves. Inequality in the rate of flow from the innervated and denervated kidneys immediately appeared when the dog, after recovery from the operation of left splanchnic resection of degeneration of the left kidney, was again put under the influence of a general anesthetic.

explained by prevention of *normal* tonic impulses from reaching *abnormally* sensitive vascular musculature.

Certain Problems Raised by Denervation Procedures Intended to Lower Arterial Pressure. One of the most important problems is whether with fall of arterial pressure adequate blood supply will be provided vital organs such as the kidneys? It was shown by Page^{39a} that marked reduction in arterial pressure may occur in patients when the fall in pressure is not sudden without change in urea clearance and, correspondingly, in blood flow. There was therefore no reason to believe that reduction in arterial pressure adversely affected the function of the kidneys. As shown especially by Freeman,²² and Freeman, Shaw and Synder,²³ the chief function of the vasomotor nerves appears to be to modify the volume flow of the blood in accordance with the needs of the body as a whole. After removal of this control by sympathectomy, blood flow is then determined largely by the metabolic demand of the local tissues.

Since denervation must perforce be performed in limited areas of the body other problems are raised which require careful study. It may be reasoned that abolition of nervous impulses in one area of the body would lead to local vasodilatation, whereas the vessels of the remainder of the body would remain constricted, leading to insufficient blood flow. Actually it has been observed that when arterial pressure falls, relaxation at least of the vessels in the eye-ground occurs. The fact that relaxation occurs in vessels other than those which have been denervated may be in part responsible for the observed fall in blood pressure following operation. Nor have any signs or symptoms been noted on clinical examination of the patients that would lead to the belief that blood flow had become inadequate in other organs.

Another problem, one of great practical importance, is whether reduction of arterial pressure by means of denervation in patients suffering from hypertension is maintained. Experiments by Magnus³⁶ on animals with normal blood pressure indicate that section of the splanchnic nerve leads to fall in pressure which lasts for days or weeks but then returns to the pre-operative level.

Removal of the entire sympathetic chain causes only a temporary lowering in arterial pressure which soon returns to normal according to Cannon.⁸ Grimson²⁶ states that complete sympathectomy will not permanently alter blood pressure of normal dogs longer than 94 to 225 days. The pressure after sympathectomy remains at a higher level than would be expected after withdrawal of all vasoconstrictor tone (*e. g.*, by spinal anesthesia). From this observation, Wilson, Roome and Grimson⁵⁶ suggest that the function is taken over by a peripheral vasoconstrictor mechanism. Studies by Page and Heuer^{40b} on patients subjected to section of the anterior nerve roots (Adson-Brown operation) demonstrated that in some of the patients the return of arterial pressure to its high level occurred

within a month or more, whereas in others it was far below the pre-operative level after 2½ years. The tendency was for a slow but definite rise in pressure level to occur. Unless return of hypertonus is very prolonged, it constitutes a serious objection to denervation procedures as therapeutic measures.

Experiments performed on animals with normal arterial pressure in which the splanchnic nerves were severed have offered little guidance in similar operations on patients with hypertension. Goldblatt, Gross and Hanzal³⁵ found that splanchnic resection neither prevented the development of hypertension nor cured it when renal ischemia was produced in dogs by constricting the renal arteries. Freeman and Page³⁶ were also able to produce hypertension in dogs in which the entire sympathetic nervous system had been removed by this method. Sympathectomy combined with denervation of the heart did not abolish the hypertension produced by Goldblatt's method. The evidence, conclusive as it is, however, is of limited value in connection with operation in man, because it is not known whether hypertension in dogs produced by renal ischemia resembles essential or nephritic hypertension.

Although most evidence is opposed to the view that the adrenal glands are directly responsible for essential hypertension, it should be mentioned that these glands are at least partially denervated by section of the splanchnic nerves (Anrep³ for example) though not completely (Cannon, Lewis and Britton).⁹ Denervation does not prevent liberation of epinephrine by humoral stimulants such as acetylcholine, histamine or peptone (Siehe).⁵⁰ Consequently, it is not possible, on the basis of contemporary evidence, to draw conclusions regarding the secretion of epinephrine in patients with hypertension following splanchnic resection.

Lastly, it must not be overlooked that smooth muscle deprived of its nerve supply in chronic experiments in animals is more sensitive to epinephrine than when normally innervated.^{15, 37} More recently Freeman, Smithwick and White³¹ have shown that the recurrence of vascular spasm after complete sympathectomy in human extremities is probably due to sensitization of the extremity to epinephrine. Degeneration of the parasympathetic supply to smooth muscle also sensitizes smooth muscle to acetylcholine.⁴⁹ The evidence thus indicates that denervated smooth muscle is sensitized to the natural chemical mediators of the nerve impulses which cause it to contract. Furthermore, Cannon and Rosenbluth¹⁰ have shown that pre-ganglionic denervation of stimulation by acetylcholine. Sympathetic ganglion cells may be regarded as innervated by preganglionic fibers. Whether such sensitization phenomena play an important part in the results of operations designed to reduce arterial pressure by means of denervation is not known.

Partial answers to these problems of varied nature are to be found in the evidence of experimental nature referred to in each case. It is obvious, however, that in the last analysis the answers depend upon careful and prolonged observation of patients. The record of each patient is therefore set forth in some detail in this study, since some of the questions which have been raised appear to be readily answered by this means.

Splanchnic Nerve Resection in Man. Probably the first to suggest splanchnic nerve resection as a treatment for hypertension were Daniélopou,¹² Bruening and Stahl⁷ and Pende⁴² in 1923. Jean³⁰ had previously recommended it for relief of pain of gastric crises. Pieri,⁴⁵ Durante¹⁷ and Santucci⁴⁸ reported on 4 patients subjected to operation. The data which were published are so meager that one cannot be certain of the results of the operation. Craig and Brown¹¹ studied some of the effects of both unilateral and bilateral resection much more carefully in 5 cases. The infradiaphragmatic approach to the nerves was employed and after section of them, the lumbar sympathetic chain was broken by removal of the first or second lumbar ganglion. Symptomatic relief was often observed, but arterial pressure was not reduced sufficiently to consider the procedure of marked therapeutic value. They showed conclusively that the operation was a relatively safe procedure and was not followed by any untoward effects. They believed that it might be of value in the early stages of the severe progressive form of essential hypertension in young persons.

The operation has been subsequently taken up by a number of surgeons, notably by Peet. Detailed studies of their cases have not as yet appeared. Fralick and Peet²¹ reported operations on 90 patients. The results have been observed in 36 cases from 5 to 22 months after operation: 5 were symptom-free and maintained normal blood pressure; 2 showed resolution of the morbid changes in the fundus due to malignant hypertension and 1 patient disappearance of angiospastic retinitis; 18 showed an appreciable drop in blood pressure and the pressure in 13 was unaffected.

The operation has been performed for other purposes than reduction of arterial blood pressure. de Takats and Cuthbert^{15a,b} reported that it increases the sugar tolerance particularly of juvenile diabetics. Temporary but marked effect of the operation in preventing the appearance of hemoglobinuria following chilling of the feet of a patient suffering from paroxysmal hemoglobinuria were observed by Ernstone and Gardner.¹⁹

Management of Patients. Blood pressure measurements were made at 9.30 A.M. daily with the patients in bed. During the pre-operative period of observation, which consisted of a month or more, they were not allowed out of bed for any purpose. After operation the patients were allowed up at will, but blood pressure measurements were made while they were in bed, hence the measurements cannot be regarded as strictly comparable with

those made before operation. Sedatives, including chloral hydrate, amylal and, less often, sodium bromide, were employed sparingly before and seldom after operation. Diets were unrestricted as to quality or amount.

Clinical Observations. Renal efficiency was measured by urea clearance and by the ability of the kidneys to concentrate urine. The urea clearance was employed, not only because it is a delicate test, but because Van Slyke, Rhoads, Hiller and Alvings²⁴ have shown that in dogs it parallels the renal blood flow. The specific gravity was measured on a 12-hour specimen voided at the end of 24 hours without fluids. Were protein present in sufficient amount to contribute to the specific gravity, a correction was made for it, that is, 0.003 subtracted from the total specific gravity for each 1% of protein (Lashmet and Newburgh²⁵). The number of formed elements in the urine was estimated by the technique of Addis.¹ Not more than 500,000 red blood cells are excreted by persons with normal kidneys. The urine protein was measured by the method of Shevky and Stafford, as slightly modified by MacKay (Peters and Van Slyke²⁶). The amount of plasma proteins was ascertained by the method of Howe.²⁷ Hemoglobin was measured by the Van Slyke and Neill²⁸ oxygen capacity method.

In some of the case histories the term "hypertensive diencephalic syndrome" is employed. By this is meant a syndrome often observed in patients suffering from hypertension consisting in its severest form of blushing which is usually confluent on the face and blotchy over the upper chest, slight perspiration over this area, lachrymation, palpitation, hypermotility of the intestine and slight rise of blood pressure (Page^{29b}). Salivation may be observed. Similar states are observed in the absence of hypertension, yet its frequent occurrence during it suggests some close association. The syndrome has been called "diencephalic" because it resembles the clinical manifestations following stimulation of the diencephalon by tumors or drugs.

Explanation of Charts. On the charts the mean normal of each value represented is drawn as a base line; the shaded areas between the base line and the points representing observations indicate the degree of deviation above or below the average normal. The brackets at the left of the scales for urea clearance, urine concentration and hematocrit, indicate the range of normal variability. The normal base line for hemoglobin varies with the patient's age and sex; the base line for each patient is located at the mean normal level for his age and sex (Table 39, p. 542; Peters and Van Slyke²⁶). Blood pressure measurements were made daily at 9.30 A.M., but are represented in the charts as averages. Each dot usually represents the averaging of from 3 to 5 blood pressure measurements. The black areas representing edema have the following significance: Height of black area in quarters of total space, 1, trace; 2, moderate pitting; 3, marked pitting; 4, general edema with ascites. Alorbid changes in the eggshadows are recorded as follows: 1, Constiction of the arterioles; 2, arteriosclerosis; 3, exudate; 4, hemorrhages; and 5, papilledema. The estimated time elapsing between onset of the disease and admission to the hospital is recorded on the lowest line of the chart, as the first number following the word "months." The other numbers in the bottom row indicate months after first admission.

Operation. The operation of splanchnic nerve resection used in this series of cases consisted in the bilateral resection of segments of the great, small and, if present and found, the smallest splanchnic nerves together with the three lower dorsal ganglia. The operative approach is above the diaphragm and is similar to that used by Lee³. Under general anesthesia a vertical incision 12 to 14 cm. long and parallel with the spine is made at the lateral border of the long muscles of the back, the mid-point of the incision lying over the previously identified eleventh rib. The incision is carried

through the fibers of the serratus muscle and the underlying fascia covering the long muscles of the spine. These are lifted from the ribs and retracted toward the mid-line. The eleventh rib is exposed and a segment approximately 6 cm. long next to the spine is resected. The intercostal muscles are carefully raised from the underlying pleura and those between the tenth and twelfth ribs divided. The pleura is carefully separated from the bodies of the vertebræ and retracted and as the dissection is carried more deeply toward the anterior margin of the vertebral column, the lower dorsal ganglia are first brought into view lying upon the anteriolateral surface of the vertebral bodies and at a deeper level the great splanchnic nerve. The latter is grasped, dissected free to the point where it penetrates the diaphragm, and a segment often 6 to 8 cm. long is resected. In the course of this dissection the small splanchnic, and occasionally the smallest splanchnic nerve, are identified together with the sympathetic fibers connecting them with the lower dorsal sympathetic ganglia. The ganglia together with the small splanchnic nerve are freed and are removed. In no instance has there been any untoward bleeding and the wounds have invariably been closed with silk without drainage.

Of the 9 patients included in this report, the bilateral operation was performed at one sitting in 5, at two sittings in 3. In 1 patient a right splanchnic resection only was performed. On 1 patient a small tear in the pleura occurred in the course of the procedure but resulting slight pneumothorax failed to provoke any untoward symptoms. With the exception of one instance of postoperative pleural effusion, there were no postoperative complications, and in all cases the wounds healed *per primam*.

Case Reports. CASE 1 (No. 9533). This patient, a 46-year-old housewife, complained of precordial pain for the past 7 months. Hypertension has commonly occurred in members of her family. An abortion was performed 9 years ago, but since then she has borne children. Temperamentally she is excitable, impulsive, often very irritable and worries over unimportant things. In the past few years she has noticed that urticaria appears on her skin when she becomes nervous. She cries easily and without apparent cause. Her memory is not nearly so accurate as formerly. She has had frequent headaches for many years. She tires easily. Precordial pain is often brought on by excitement and is said to be relieved by nitroglycerine. Menstruation became irregular 5 years ago, and stopped 2 years ago. Her blood pressure was found normal 9 years ago but was elevated a year later during her first pregnancy. Two years later arterial pressure varied from 185/95 to 220/125 mm. Recently, the subjective symptoms have become so severe that she has been incapacitated. She was kindly referred to us by Dr. Maurice T. Root of West Hartford, Conn.

Physical examination showed that she was a thin, high-strung woman appearing chronically ill. The eyegrounds were normal. Tonsils had been cleanly removed. Heart rate was 88. A soft systolic murmur was heard at the apex. Peripheral vessels were thickened (Grade 1). Roentgen ray examination showed the cardiac silhouette to be normal. The electrocardiogram was normal.

Although there appeared to be a large neurotic element associated with hypertension in this patient, the arterial pressure did not fall under complete bed rest and mild sedatives. During a month of observation it varied from 212 to 166 mm. systolic and 120 to 100 mm. diastolic. The average pressure was 190/110 mm. Since no significant relief from the subjective symptoms had been secured it seemed desirable to ascertain the effects of bilateral splanchnic resection.

[illegible][illegible]

On June 19, 1935, right supradiaphragmatic splanchnic resection was performed and left supradiaphragmatic splanchnic resection on July 1. Except for some stiffness of the muscles of the back, the postoperative course was uneventful. Blood pressure varied rather widely for a few days after operation, but became stabilized at an average of 178/110 mm. during the 21 days rest in the hospital after operation. It varied from 190. to 168 mm., systolic; and 118 to 96 mm., diastolic. The subjective symptoms were moderated but did not disappear. Headaches and precordial pain were much less severe, but emotional instability continued unabated. Arterial pressure 1½ years later was about the same as before operation. She felt somewhat better in that she was less nervous and had fewer headaches.

Summary of Case 1. A woman aged 46 with essential hypertension probably beginning during her first pregnancy 8 years ago, exhibited many signs and symptoms of a highly developed neurosis. Splanchnic resection lowered arterial pressure temporarily, but within 6 months it has resumed its pre-operative level. The arterial pressure was about the same 1½ years later but headaches were less frequent, precordial pains had disappeared and she tired less easily. It was our opinion that she had been aided mentally by the operation without marked physical change.

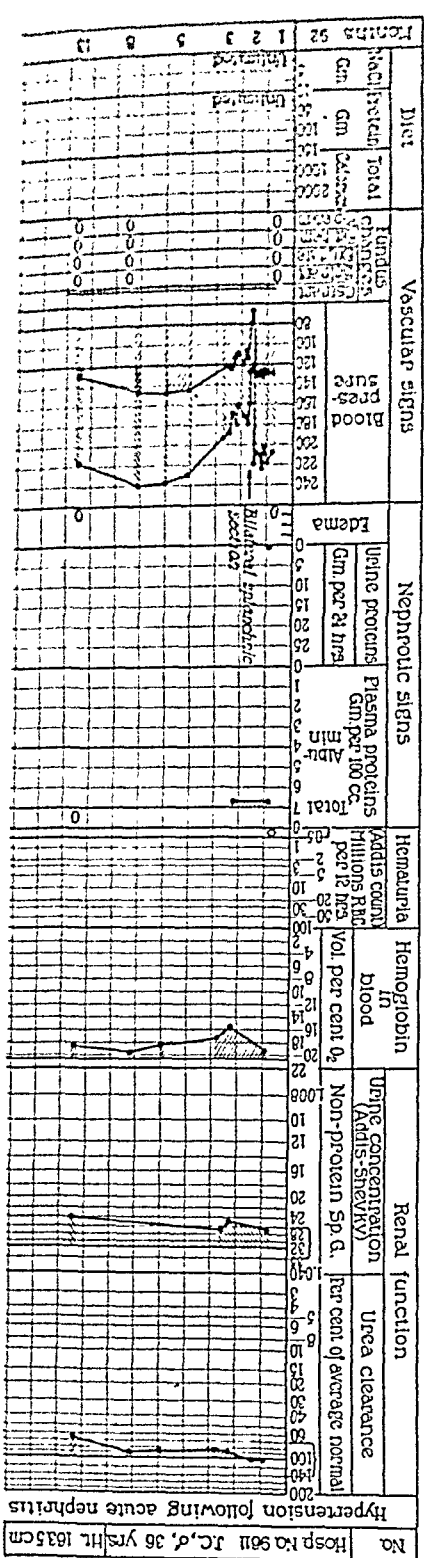
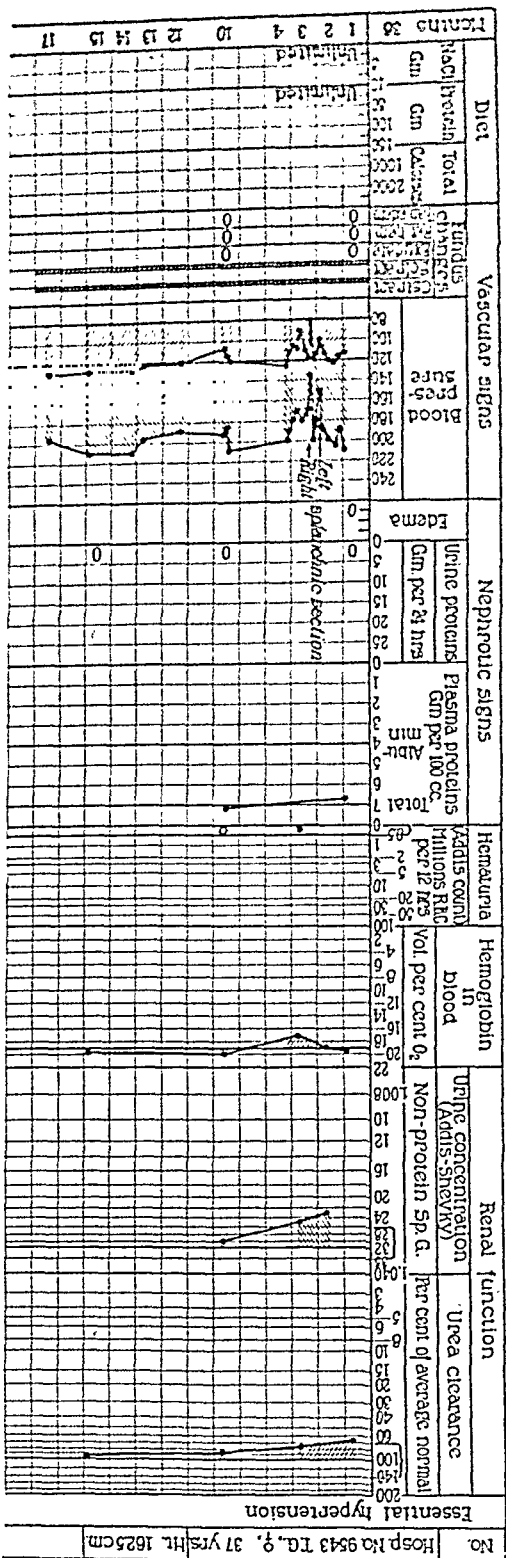
CASE 2 (No. 9685). This patient, a 48-year-old Swiss housewife, complained of nervousness and irritability. Her past health was always excellent. She had hot flashes, spots before her eyes, cried and blushed easily. Her menstruation was regular, but was always rather scanty. She noticed no change in it.

On physical examination she was found to be very overactive. There was a marked flush over her face and the skin of her face and hands and feet was moist. The arterioles of the fundi showed Grade 2 constriction and no perivasculitis. They were not tortuous. The veins were dilated (Grade 2) with very slight if any arteriovenous compression. The thyroid gland was diffusely enlarged (Grade 1). The heart was very slightly enlarged (Grade 1). There were no murmurs; A_2 and P_2 were not accentuated. Peripheral vessels were not thickened. Superficial and deep reflexes were hyperactive. Roentgen ray of the skull showed Grade 1 pineal calcification and a small but normal sella. The blood pressure ranged from 260 to 210 mm. systolic, and 130 to 106 diastolic, with an average pressure of 230/120 mm.

On December 14, 1935, bilateral supradiaphragmatic splanchnic resection was performed. Except for some abdominal distention and difficulty in voiding, the postoperative course was uneventful. Within 10 days the patient was up and about. The basal metabolic rate before operation was +24; 2 weeks after operation it was -9. There was no change in renal efficiency. Her nervousness continued. Blood pressure varied from 160 to 194 systolic and 96 to 120 diastolic. The average was 180/110 mm. during the period of hospitalization of 1 month, but 9 months after operation it has risen to 220/122 mm.

Five months after operation the symptoms and signs of adenomatous goiter were sufficiently marked to justify subtotal thyroidectomy. One month before this operation the basal metabolism was +22 and it fell to +6 2 weeks after operation. No significant change in arterial pressure occurred. She appeared to be less restless.

Summary of Case 2. This 48-year-old woman suffered from essential hypertension and adenomatous goiter. Renal function



was normal. One year after splanchnic resection and 9 months after subtotal thyroidectomy, arterial pressure was unchanged from its pre-operative level. She is less nervous than before thyroidectomy, but otherwise there has been little change in her clinical condition.

CASE 3 (No. 9543). A 37-year-old housewife, complained of weakness, excessive nervousness, insomnia and palpitations for 2½ years. She was irritable, impulsive and worried much. She blushed and cried often without apparent reason. Since the onset of the present illness there was a decrease in menstrual flow.

The present illness was first recognized 3 years ago. She noticed swelling of the ankles during the fifth month of her first pregnancy. Two months later she had a miscarriage. Her blood pressure was said to be elevated and protein was found in the urine. Hypertension has persisted.

The patient was a small, nervous woman, appearing very restless. The disks of the eyegrounds were slightly hyperemic (Grade 1) the arterioles were slightly tortuous (Grade 1) and in a number of places there was slight arteriovenous compression. The thyroid gland was not palpable. The heart was not enlarged and the sounds were of good quality. There was a fine tremor to the outstretched fingers, but no other signs of Graves' disease. The deep reflexes were overactive but equal, on both sides. Roentgen ray revealed that the sella turcica was normal. The basal metabolic rate was +25% on admission and +25% 16 days later. The blood pressure varied from 220 to 184 systolic and 140 to 104 diastolic, and averaged 200/120 mm. during 23 days of rest in bed. The Wassermann reaction was negative.

On June 28, 1935, splanchnic resection was performed. The post-operative course was uneventful. For a period of 3 to 4 months she felt better; symptoms and signs of the "hypertensive diencephalic syndrome" continued unchanged. One year after operation the arterial pressure averaged 194/114 mm. and she again complained of palpitations, restlessness and extreme nervousness.

Summary of Case 3. This 37-year-old woman suffered from essential hypertension. It may have begun during her first pregnancy. The disease appears to be quite benign. Bilateral splanchnic resection was associated with a moderate fall in arterial pressure and a feeling of well-being which lasted only a few months. Now 1½ years after operation, the pressure is at its pre-operative level and restlessness, nervousness and palpitations have returned.

CASE 4 (No. 9611). This 35-year-old man complained of dizzy spells, palpitations and shortness of breath on exertion for 3 months. He suffered possibly from acute nephritis with slight hypertension 8 years ago. Arterial pressure 8 months ago was found to be 240/138 mm.

The patient was found to be a short, thin, wiry man not appearing ill. The arterioles of the fundi were constricted (Grade 1), but there was no perivascular reaction or tortuosity. The tonsils were chronically inflamed. The heart was not enlarged; its rate was regular but rapid with a soft blowing systolic murmur at the apex. Peripheral vessels were thickened (Grade 2). The sella turcica appeared normal to Roentgen ray. The systolic pressure varied from 226 to 200; the diastolic from 140 to 116 mm.; average, 210/130 for a month's period. This patient appeared well suited for operation since no renal damage was present, cardiac enlargement had not occurred and the retinal changes were minimal.

[illegible]

Bilateral supradiaphragmatic splanchnic resection was performed on October 17, 1935. Convalescence was uneventful. Arterial pressure after a marked fall slowly rose to an average of 182/118 (systolic 194 to 170 mm.; diastolic 124 to 110 mm.) during a period of 4 weeks. One year after operation the average pressure was 218/130. He no longer complains of dizzy spells or palpitations, but he becomes fatigued very easily.

Summary of Case 4. This 35-year-old man had essential hypertension with slight morbid vascular change and normal renal efficiency. Splanchnic resection caused a fall in arterial pressure which lasted for 2 months. It then regained its original level. The operation does not appear to have influenced the course of the disease.

CASE 5 (No. 9679). A 25-year-old telephone operator complained of severe headaches for the past 3 years. She had always been well until the present illness, except for scarlet fever at 4 years of age and typhoid at 16. Appendectomy was performed 9 years ago, and tonsillectomy 6 months ago. She was impulsive and irritable, and easily fatigued. In the past 3 years, she noticed that she cried spontaneously and also that blushing was marked. Menstruation was scanty but regular. She was oversexed. Five years ago, it was known that her blood pressure was normal; 3 years ago it was found to be slightly elevated and 1 year ago was found to be 200/140. She noticed that in the past 5 months on climbing one flight of stairs she became short of breath. Her ankles have not swelled.

Physical examination showed that the patient was highly nervous. The skin over the face and upper chest was covered with perspiration and there was a mottled blush over this area. The arterioles of the ocular fundi showed sausage-shaped constriction (Grade 2) with slight perivascular reaction (Grade 1). There was arteriovenous compression (Grade 2) in certain places. The veins were not unusual and there were no hemorrhages or exudates. There was a marked carotid pulsation in the neck. The thyroid gland was diffusely enlarged (Grade 1) but it was soft and there were no nodules. The heart rate was 80 to 92 and there was a short systolic whiff at the apex. The aortic second sound was markedly accentuated. Roentgen ray of the chest showed the total transverse diameter of the heart 11.2 cm., the internal chest diameter 25.5 cm. There was moderate elongation of the aorta without widening. A Roentgen ray photograph of the skull showed that the calvarium was moderately thickened and there was especially heavy calcification over the frontal bones. There was apparent erosion of the posterior clinoid process. The pituitary gland itself was not encroached upon. The pineal gland was calcified (Grade 1). The cold pressor test showed a response of 28 mm. systolic and 12 mm. diastolic. The blood pressure varied from 206 maximum to 170 minimum systolic, and maximum diastolic of 126, minimum 106. The average pressure was 180/120, over a period of 1 month in bed. The basal metabolism was -2.6%.

Splanchnic nerve resection was performed on the right side. The nerve was found to be unusually large. The convalescence was uneventful and within 6 days she was up and about. The blood pressure was somewhat lower; during the period of 24 days after operation it varied from 140 to 170 systolic, and 90 to 108 diastolic (mean pressure, 160/100). Within 3 months the arterial pressure had returned to its pre-operative level. Headaches have been reduced in intensity and frequency (10 months after operation) and this appears to have been the only benefit derived from operation.

Summary of Case 5. This 25-year-old patient suffered from mild essential hypertension of 2 years' duration. Headaches and easy

Time	Diet			Funds changes	Vascular signs		Nephrotic signs			Hematuria RBC count per 12 hrs	Hemoglobin in blood Vol. per cent of	Renal function	
	Protein Gm	Calories Kcal	Total Gm		Blood pressure	Idema	Urine proteins Gm per 24 hrs	Plasma proteins Gm per 100 cc	Albumin in			Urine concentration (Auer-Scheyky)	Non-protein SP. G.
1	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
2	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
3	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
4	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
5	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
6	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
7	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
8	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
9	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
10	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
11	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
12	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
13	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
14	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
15	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
16	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
17	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
18	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
19	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
20	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
21	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
22	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
23	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
24	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
25	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
26	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
27	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
28	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
29	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100
30	10	100	110	100/60	100	0	0	7.0	4.0	100	15	1.02	100

Essential hypertension

Hosp No 5582 T15, 9, 34 yrs HL 160 cm

Date	Vascular signs		Nephrotic signs		Hematuria		Hemoglobin in blood		Renal function	
	Blood pressure	Edema	Urine proteins gm per 24 hrs	Plasma proteins gm per 100 cc	Acid count million per 12 hrs	Vol. per cent	Urine concentration (Acidic specificity)	Non-protein N per cent of average normal	Urea clearance	Urea clearance per cent of average normal
1	120/80	0	0	7.5	10	10	10	10	10	10
2	120/80	0	0	7.5	10	10	10	10	10	10
3	120/80	0	0	7.5	10	10	10	10	10	10
4	120/80	0	0	7.5	10	10	10	10	10	10
5	120/80	0	0	7.5	10	10	10	10	10	10
6	120/80	0	0	7.5	10	10	10	10	10	10
7	120/80	0	0	7.5	10	10	10	10	10	10
8	120/80	0	0	7.5	10	10	10	10	10	10
9	120/80	0	0	7.5	10	10	10	10	10	10
10	120/80	0	0	7.5	10	10	10	10	10	10
11	120/80	0	0	7.5	10	10	10	10	10	10
12	120/80	0	0	7.5	10	10	10	10	10	10
13	120/80	0	0	7.5	10	10	10	10	10	10
14	120/80	0	0	7.5	10	10	10	10	10	10
15	120/80	0	0	7.5	10	10	10	10	10	10
16	120/80	0	0	7.5	10	10	10	10	10	10
17	120/80	0	0	7.5	10	10	10	10	10	10
18	120/80	0	0	7.5	10	10	10	10	10	10
19	120/80	0	0	7.5	10	10	10	10	10	10
20	120/80	0	0	7.5	10	10	10	10	10	10
21	120/80	0	0	7.5	10	10	10	10	10	10
22	120/80	0	0	7.5	10	10	10	10	10	10
23	120/80	0	0	7.5	10	10	10	10	10	10
24	120/80	0	0	7.5	10	10	10	10	10	10
25	120/80	0	0	7.5	10	10	10	10	10	10
26	120/80	0	0	7.5	10	10	10	10	10	10
27	120/80	0	0	7.5	10	10	10	10	10	10
28	120/80	0	0	7.5	10	10	10	10	10	10
29	120/80	0	0	7.5	10	10	10	10	10	10
30	120/80	0	0	7.5	10	10	10	10	10	10
31	120/80	0	0	7.5	10	10	10	10	10	10
32	120/80	0	0	7.5	10	10	10	10	10	10
33	120/80	0	0	7.5	10	10	10	10	10	10
34	120/80	0	0	7.5	10	10	10	10	10	10
35	120/80	0	0	7.5	10	10	10	10	10	10
36	120/80	0	0	7.5	10	10	10	10	10	10
37	120/80	0	0	7.5	10	10	10	10	10	10
38	120/80	0	0	7.5	10	10	10	10	10	10
39	120/80	0	0	7.5	10	10	10	10	10	10
40	120/80	0	0	7.5	10	10	10	10	10	10

fatigability were the most marked symptoms. Unilateral splanchnic resection reduced the arterial pressure temporarily, but within 3 months it returned to the pre-operative level. The only benefit derived from operation appeared to be reduction in the frequency and intensity of the headaches.

CASE 6 (No. 9582). A 34-year-old Italian housewife complained of headaches for about 10 years. They have become very severe and occur almost every day. Five years ago her second baby was born, and during the last months of pregnancy she developed edema, which disappeared after delivery. She was told that she had hypertension at that time. She noticed palpitations for the first time 4 years ago. In the past 2 years, signs and symptoms characteristic of the "hypertensive diencephalic syndrome" have become increasingly prominent. She is overexcitable, irritable and worries greatly.

The eyegrounds showed moderate papilledema. The arterioles were constricted, in many places to the point of complete obliteration, and the veins were dilated (Grade 3). There were no hemorrhages nor exudate. The thyroid gland was diffusely enlarged (Grade 1) but no other physical signs of hyperthyroidism were found. There was a marked systolic thrust in the jugular notch. The heart rate was very rapid. The sounds were of good quality and there were no murmurs. The electrocardiogram showed the T-wave upright in Lead I, and inverted in Leads II and III. Conduction time was 0.12 seconds. Sinus tachycardia was present and also intra-ventricular heart block. Roentgen ray examination showed the sella turcica to be normal. The basal metabolic rate 4 months ago was +33, and at present it is +32 as measured on two occasions. The cold pressor test showed a rise of 8 mm. systolic and 12 mm. diastolic. The blood pressure varied from 192 to 232 mm. systolic and 112 to 144 mm. diastolic, the average pressures being 216/126 mm. during 26 days in bed.

Bilateral supradiaphragmatic splanchnic resection was performed on November 5, 1935. Postoperative convalescence was uneventful, except for a small left pleural effusion directly following the operation. On the tenth day the patient was up. There was a rather remarkable change in the fundi. Papilledema had markedly regressed. The arterioles were of normal caliber. There was no arteriovenous compression. The veins were of normal size. There was no exudate or hemorrhage. The blood pressure averaged 150/90 over a period of 5 weeks after operation with a systolic maximum of 170 and minimum of 138; diastolic maximum was 106, minimum 78. Within 5 months the blood pressure returned to the pre-operative level. The frequency and severity of the headaches were much reduced for a period of 1 year after operation. The eyegrounds remained normal during that period.

Summary of Case 6. This patient suffered from moderately severe essential hypertension. The most remarkable feature of the case was the occurrence of papilledema and severe arteriolar constriction in the eyegrounds. Following operation, after a fall lasting several months, the blood pressure level returned to very nearly the pre-operative level. In spite of this, the morbid fundus changes disappeared and after 1 year the eyegrounds were still normal. Moderate subjective improvement occurred.

CASE 7 (No. 9651). A 25-year-old salesman had epileptic attacks for 2 years, and about twice a month since then. It is impossible to date the onset of his hypertension. It was found at the time of onset of the epilepsy. Headaches were the only symptom and these were not severe.

Physical examination showed papilledema of both nerve heads. The disks were hyperemic and the edges blurred. The arterioles in many places were markedly constricted. Many of the arterioles showed corkscREW distortion. There was sclerosis (Grade 4). Temporal to the right disk was a small hemorrhage. The tonsils had been removed. The heart was boot-shaped. There appeared to be slight widening at the base. There was an aortic diastolic murmur. Peripheral vessels were slightly thickened. Deep reflexes were hyperactive.

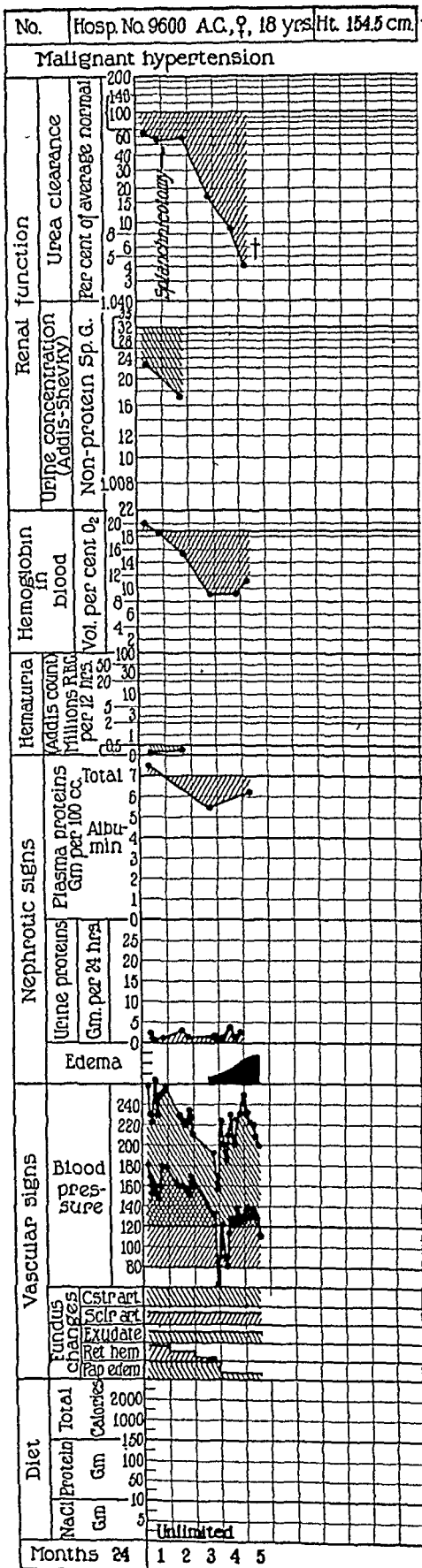
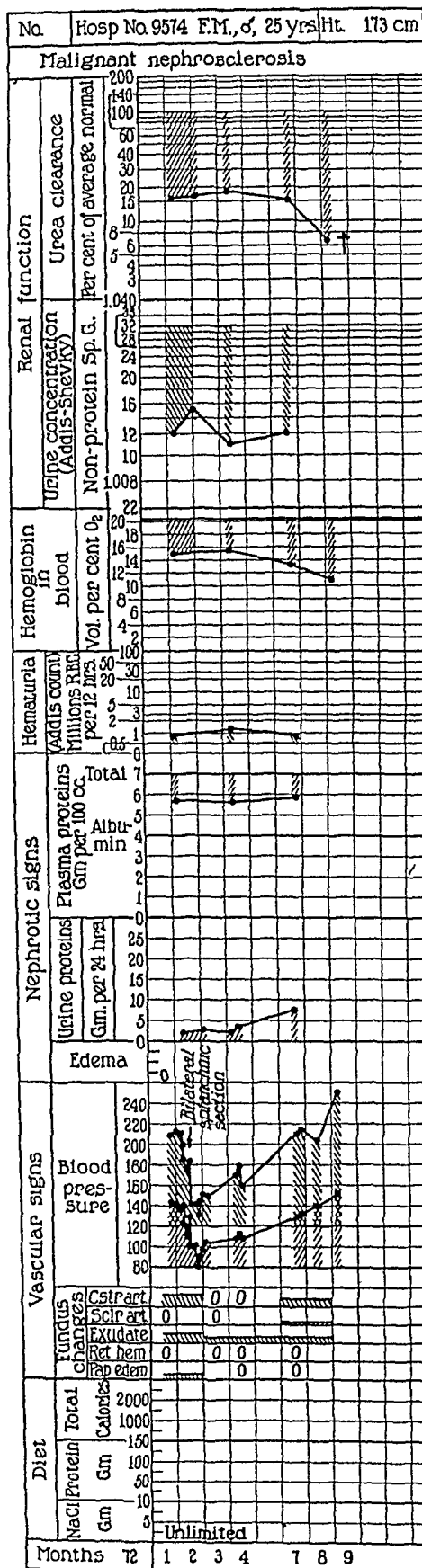
Röntgen ray of skull showed that the pineal gland was calcified (Grade 1); the sella was normal. Röntgen ray of the chest showed the aorta to be widened and the lungs normal. The electrocardiogram showed that the T waves in Leads I and II were inverted. Arterial pressure varied from 240 mm. to 204 mm. systolic and 140 mm. to 122 mm. diastolic (average 226/134 mm.) during a period of 21 days in bed.

On November 26, 1935, left splanchnic resection was performed. There was no change in his average blood pressure following operation. On December 10, right splanchnic resection was performed. The operation was complicated by postoperative hemorrhage, which necessitated reopening of the wound, but following this the course was not remarkable. There was a marked fall in hemoglobin to 13.54 vol. %, and a very slight fall in urea clearance. Arterial pressure varied from 109 to 235 mm. systolic and 110 to 140 diastolic (average 200/130 mm.) during a period of 38 days in bed. Within 2 months, the pressure had reached the pre-operative level. He had two attacks during the convalescence suggestive of epilepsy.

Summary of Case 7. This was a case of early malignant hypertension in a 25-year-old man, complicated by epilepsy. Bilateral splanchnic resection produced a temporary sharp fall in arterial pressure but within 2 months it had regained its pre-operative level. During the month following operation the papilledema disappeared. The symptoms and signs of the epilepsy were unchanged.

Case 8 (No. 9574). A 25-year-old male clerk, complained of headaches for 2 months. He had always considered himself healthy. In 1931, tonsillectomy was performed. He noticed recently that he cries without reason, and often has palpitations of the heart. There has been slight dyspnea on exertion. At the age of 17, his blood pressure was said to have been a little elevated, but he paid no attention to this, and it was not until 8 years later that it was again measured because of rather constant headaches. It was found to be moderately elevated.

Fundus examination showed Grade 1 papilledema of the right disk as well as Grade 1 hyperemia. The arterioles in both eyes were constricted (Grade 3); but certain of them showed only slight constriction. In some places there was rather marked arteriovenous compression. The veins were dilated (Grade 2). Diffusely scattered throughout the retina, but especially concentrated in a ring around the disk were small, discrete patches of hard white exudate. There were no hemorrhages. The thyroid gland was just palpable. The heart sounds were of good quality. Peripheral vessels were definitely thickened (Grade 2 to 3). The blood pressure varied from 152 to 210 mm. systolic and 120 to 140 diastolic (average 198/136 mm.). The electrocardiogram showed that the T waves were diphasic in Lead I, upright in Lead II, and diphasic in Lead III; conduction time was 0.19 seconds. The rhythm was normal. The sella turcica was normal as shown by Röntgen ray photographs. The Wassermann and Klein reactions were negative. It was our impression that this was a case of rapidly advancing, malignant nephrosclerosis. Since his physical condition was excellent, except for the



low renal efficiency, it was believed that reduction of the elevated arterial pressure might prolong life.

Bilateral splanchnic resection was performed on July 11, 1935. Following operation small pleural effusions occurred, but these soon disappeared. Six weeks later, moderate regression of the fundus changes had occurred, but there was no improvement in renal function. Arterial pressure varied from 170 to 190 mm. systolic and 106 to 118 mm. diastolic. Six months after operation the pressure had returned to its original level and retinal changes were again present. Two months later death occurred from renal and cardiac failure.

Summary of Case 8. This 25-year-old man suffered from malignant hypertension with markedly reduced renal function. In spite of this, his general clinical condition was excellent, and he was almost without symptoms. Since arterial pressure was high and apparently causing morbid vascular changes, bilateral splanchnic resection was performed in an effort to reduce the pressure. Reduction occurred for a period of 3 months and definite regression of the pathologic changes in the eyegrounds was observed. Renal efficiency did not improve. Within 6 months, the arterial pressure rose to its pre-operative level and the disease resumed its progress ending with renal and cardiac failure 7 months after operation.

CASE 9 (No. 9600). An 18-year-old girl considered herself healthy until 2 years ago when severe headaches began. Shortly thereafter, she had a convulsion. Her blood pressure was measured and found to be 140 mm. Headaches became more severe and were associated with nausea and vomiting. They were often followed by attacks suggesting epilepsy. Tingling in the hands and feet was noted, shortly followed by stiffening of the muscles of the body. She became stuporous and moderately cyanotic. The attack was usually terminated by vomiting. Arterial pressure taken shortly after it was 290/186 mm. on one occasion. The attacks usually appeared during the week preceding menstruation and seldom occurred until the next period. Recently they have increased in frequency. Now they may occur at any time. She has never had any signs or symptoms suggestive of the "hypertensive diencephalic syndrome."

Physical examination showed her to be well-developed and not appearing ill. Very marked papilledema was observed in both disks. The arterioles were irregular and showed moderate perivascular reaction (Grade 2). In many places they were obliterated. In some sectors the small arterioles were surrounded by hemorrhages. Hard white exudate occurred in small patches throughout the fundi. In the left fundus there was an early stellate figure. The heart was slightly enlarged (Grade 1).

Roentgen ray picture of the skull showed that the sella was flattened and bridged across. Spinal fluid pressure was 220 mm. of water, and arterial pressure was 232/160 mm. Blood and spinal fluid Wassermann reactions were negative.

She had a number of attacks such as those described above while in the hospital. It was difficult to be certain that the rise in arterial pressure was paroxysmal in nature because pressure measurements could be taken only at the termination of the attack after she had undergone severe physical strain. During the pre-operative period of observation arterial pressure averaged 242/160 mm.; systolic range, 264 to 210 mm.; diastolic 186 to 146 mm.

On October 1, 1935, bilateral splanchnic resection was performed. Throughout the operation the blood pressure remained markedly elevated. This was an unusual occurrence as all of the other patients showed marked reduction.

Convalescence was rapid and uneventful. Eighteen days after operation she suffered an attack strongly suggestive of a transient apoplexy. Right-sided weakness of the hand and foot appeared and she was unable to speak. This passed off in about an hour. Retinal changes were more marked than before operation and she complained of blurred vision. Arterial pressure averaged 230/158 mm. for a month after operation.

She was readmitted 2 months after operation, in the meantime having had an attack of acute cardiac failure and become totally blind. Papilledema was extreme with almost complete obliteration of the arterioles. It appeared that the blood supply to the retina had been choked off. All signs and symptoms pointed to cardiac and renal failure. She died 4 months after operation.

Autopsy (Dr. C. P. Rhoads, 3 hours after death) confirmed the clinical diagnosis. The kidneys in particular showed marked morbid changes. The intima of the arterioles was extremely thickened leading almost to occlusion. The glomerular basement membrane was uniformly very marked thickened. Some increase in vascular endothelial nuclei was observed. Diffuse increase in interstitial connective tissue had occurred. The tubules were atrophied and dilated.

A plum sized tumor was found in the region of the right adrenal. Its appearance on microscopic examination was typical of a neuroblastoma. Trichloroacetic acid and aqueous extracts of the tumor were prepared and tested on anesthetized cats for epinephrine. None was found, though control extracts prepared from the patient's adrenal glands showed large amounts.

Summary of Case 9. This 18-year-old girl suffered from malignant hypertension which ran its course in 2 years. The disease was characterized by the early appearance of renal and cardiac failure and blindness. Bilateral splanchnic resection appeared to have no influence upon the course of the disease or its signs and symptoms.

Summary. 1. Splanchnic nerve resection with interruption of the thoracic sympathetic chain was performed on 9 patients. Six of them were cases of essential hypertension varying in severity from mild to severe and in age from 25 to 48 years. Of the other 3, 1 (aged 25) suffered from early malignant hypertension and the remaining 2 (aged 18 and 25) from severe malignant hypertension.

2. Splanchnic nerve resection was well borne in all patients, and there have been no complications or fatalities. We have been unable to detect that the patients have been harmed by the operation. The reduction in arterial pressure which occurred following operation was marked but within 6 months it had returned to the pre-operative level in all patients. Subjective improvement consisting of lessening in frequency and severity of headaches, ease of fatigue, nervousness, tenseness and irritability, occurred in 6 of the patients with essential hypertension, but in 3 improvement lasted less than a year. Improvement in those with malignant hypertension was transient.

3. Renal efficiency was unaffected by the operation. It also appeared to have no marked effect on the heart as judged by electrocardiographic records or Roentgen ray photographs (Table 1). No consistent change was observed in the pressor response to immersion of the hand in cold water (Hines and Brown test²⁷). In 1 case of essential hypertension and 2 cases of malignant hypertension papilledema disappeared but reappeared in the latter cases within several months. Reduction in intensity of the constriction in the retinal arterioles occurred in all of the cases except 1 with malignant hypertension (similar cases are reported by Fralick and Peet²¹) demonstrating that arteriolar relaxation occurs in regions other than those denervated. In most of the patients constriction has returned after several months.

4. The therapeutic results in this small but representative group of cases do not appear to us to be encouraging.

TABLE 1.—ELECTROCARDIOGRAPHIC AND CARDIAC SHADOW RECORDS OF PATIENTS BEFORE AND AFTER SPLANCHNIC RESECTION.

Case No.	Time in weeks before and after operation.	Electrocardiogram.				Time in weeks before and after operation.	Measurement of heart on Roentgen ray plate.	
		T ₁ .	T ₂ .	T ₃ .	Conduction time, in seconds.		Transverse diameter, cm.	Internal diameter of chest, cm.
1	6 before	+	+	+	0.19	3	11.6	24.7
	32 after	+	+	+	0.16	52	11.4	23.3
2	3 before	+	+	—	0.15	3	12.5	24.3
	32 after	+	+	—	0.15	..	12.4	24.4
3	3 before	+	+	+	0.18	6	12.0	22.4
	60 after	+	+	+	0.14	..	13.2	23.5
4	3 before	+	+	+	0.12	3	10.6	23.5
5	2 before	+	+	+	0.14			
	20 after	+	+	—	0.13			
6*	12 before	+	—	—	0.15	2	12.2	23.5
	40 after	+	—	—	0.12	40	12.5	23.0
7	3 before	—	—	+	0.15	3	15.5	32.0
8	3 before	±	+	±	0.19	1	14.5	26.5
	22 after	±	+	+	0.15	22	14.8	26.9
9	1 before	+	+	+	0.15	2	10.2	23.5
	8 after	+	+	+	0.10	8	14.1	25.7

* Intraventricular heart block present.

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BOOK REVIEWS AND NOTICES.

PHYSICAL THERAPEUTIC METHODS IN OTOLARYNGOLOGY. By ABRAHAM R. HOLLENDER, M.D., F.A.C.S., Associate in Laryngology, Rhinology, and Otology, University of Illinois College of Medicine; Fellow of the American Academy of Ophthalmology and Otolaryngology. Pp. 442; 189 illustrations. St. Louis: The C. V. Mosby Company, 1937. Price, \$5.00.

The author is to be congratulated on both his presentation and choice of collaborators. The literature on otolaryngology of today is so filled with references to certain types of physical therapy that intelligent reading demands some knowledge of these procedures. In this book all such methods are clearly explained and an attempt has been made to evaluate their worth. A complete bibliography is included which will be of great help to the busy otolaryngologist who wishes to secure more detailed information upon any particular one of the subjects discussed.

K. H.

THE MANAGEMENT OF OBSTETRIC DIFFICULTIES. By PAUL TITUS, M.D., Obstetrician and Gynecologist to the St. Margaret Memorial Hospital, Pittsburgh; Consulting Obstetrician and Gynecologist to the Pittsburgh City Homes and Hospital, Mayview, and to the Homestead Hospital, Homestead, Pa. Pp. 879; 314 illustrations, including 4 color plates. St. Louis: The C. V. Mosby Company, 1937. Price, \$8.50.

THIS new work, representing an effort to aid practical physicians in meeting and contending with obstetric emergencies, proceeds at once concisely to the recognition and treatment of abnormal conditions. The book opens with an interesting discussion of the present trends in obstetric practice and problems of the day, such as maternal welfare, training of students and physicians in obstetrics, the trend toward specialization in practice and the increasing hospital service in many areas.

The text begins with an excellent discussion of the causes and factors and treatment of sterility which is followed by a section on the difficulties in diagnosis of pregnancy. Following chapters on the complications of pregnancy, labor and puerperium and obstetric operations, the accidents, injuries and abnormal conditions of the newborn are discussed. The book closes with 4 chapters on general topics: the preparation for obstetric operations, the pre-natal, postpartum, postoperative care of the obstetric patients, a separate chapter on the various forms of obstetric analgesia, anesthesia, technique of each and a final chapter on supportive treatment describing various types of intravenous injections and the technique of blood transfusion.

Titus reports 49.2% of pregnancy in his cases of relative sterility. His impression of treatment by means of hormonal extract is that the effect is uncertain, the underlying basis not clearly understood, the cost prohibitive, and distinct harm may result in some instances. The author regards the treatment of varicose veins during pregnancy as unnecessary except in rare instances. He does not favor myomectomy during pregnancy, but would perform the operation after Cesarean section on account of the frequent occurrence of necrobiosis. He supports Porro Cesarean section for generalized peritonitis as a result of a complicating appendicitis. Under the treatment of syphilis he states, "Syphilis in the pregnant woman should be treated as vigorously as in the non-pregnant woman." There

are many workers who feel that the treatment should consist only in a sufficient effort to prevent the child from being born a congenital syphilitic. The author expresses an extremely radical opinion on the treatment of hydatid mole and chorioepithelioma.

The author recommends breaking up the breech even before full dilatation occurs, but does not follow this by any effort of traction. Braxton-Hicks version is recommended for placenta prævia in the home. Very careful analysis of the individual case in the hospital should determine which of the described treatments is to be chosen. The use of blood transfusion in various hemorrhage conditions is stressed. Emphasis is placed on the recognition of contracted pelvis as the basis of proper management of labor in such instances. The subject of pelvimetry, clinical and roentgenologic, is thoroughly presented as is also the management of dystocia from contracted pelvis.

Obstetric operations are described in detail with good accompanying illustrations. The low cervical section is preferred and the author mentions that both in this and classical section it is his practice uniformly to pack the uterus, using the De Lee shuttle with gauze attached. In his consideration of puerperal infection, the author describes the technique used in his hospital and makes the statement that complete masking of all patient contacts and the vaginal instillation of antiseptics has reduced his maternal morbidity from 18.9 to 8.92%. His well-known theories and treatment of hyperemesis gravidarum and toxemia of late pregnancy are succinctly set forth.

Space forbids a discussion of the author's personal opinions as to many other obstetrical complications. His teaching and technique should be of interest, not only to the general practitioner in quickly available directions in any emergency, but to the hospital chief who may wish to compare his preferences under such circumstances with those here so clearly and tersely set forth.

P. W.

MODERN UROLOGY. In Original Contributions by American Authors. Vol. I. General Considerations—Diseases of Penis and Urethra—Diseases of Scrotum and Testicle—Diseases of Prostate and Seminal Vesicles. Vol. II. Diseases of the Bladder—Diseases of the Ureter—Diseases of the Kidney—Radiation Therapy of Tumors of the Genito-urinary Tract. Edited by HUGH CABOT, M.D., LL.D., C.M.G., F.A.C.S., Professor of Surgery, The Mayo Foundation, Graduate School of the University of Minnesota, and Consulting Surgeon to The Mayo Clinic, Rochester, Minn; formerly Dean and Professor of Surgery in the Medical School of the University of Michigan, Ann Arbor, Mich. Pp., Vol. I, 951; Vol. II, 862. Illustrations: Vol. I, 546 and 12 plates (some in colors); Vol. II, 374 and 9 colored plates. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, \$20.00.

THE last edition of this encyclopedic work appeared 12 years ago. So many changes have taken place that the present edition is practically a new work, to which 35 American authors have contributed. The first volume deals with general considerations, such as methods of diagnosis in lesions of the urinary tract, the use of the cystoscope, and syphilis of the genito-urinary organ, and with the diseases of the penis, the urethra, the scrotum, testicle, prostate and seminal vesicles. In the second volume are discussed the bladder, the ureters, kidneys, and the tumors of the genito-urinary tract. To illustrate the scope of the work, the contents of the section on the kidney may be cited: there are chapters on the embryology, anatomy, physiology and function of the kidney; on modern tests of renal function; on anomalies of the kidney, hydronephrosis, movable kidney, injuries to the kidneys; infections (including separate chapters on

schistosomiasis, renal echinococcosis, and tuberculosis), stones in the kidney and ureters, and of tumors of the kidneys.

Each chapter is profusely illustrated by well-selected photographs, diagrams and drawings, many of the later being remarkable for their combination of artistic excellence and strict adherence to anatomical detail.

It need scarcely be stated that these books are an invaluable reference work for the general practitioner, as well as a working tool for the specialist.

B. L.

ST. THOMAS'S HOSPITAL REPORTS, SECOND SERIES, VOL. I. Editors: PROF. O. L. V. S. DE WESSELOW, MR. C. MAX PAGE, assisted by MR. N. R. BARRETT, DR. J. ST. C. ELKINGTON, DR. A. J. WRIGLEY. Pp. 199; illustrated (3 in color). London: St. Thomas's Hospital, 1936. Price, 7s. 6d.

THIS, the "senior Borough hospital" of London, was the first—by a few months—to issue a volume of reports, 100 years ago. After various vicissitudes, the reports in 1870 began a single volume annually which latterly "have mainly consisted of arid statistical tables." The present volume is the first of a new type "which will aim in a series of original articles at a reflection of recent work carried out in the Hospital." It will be interesting to see how well and how long it can survive the inevitable trend of the staff members to present their best work in the recognized journals of wider distribution. If the excellence of the 20 articles that comprise the first volume is maintained, its success should be assured.

E. K.

UROLOGICAL ROENTGENOLOGY. By MILEY B. WESSON, M.D., Ex-President, American Urological Association, and HOWARD E. RUGGLES, M.D., Roentgenologist to the University of California Hospital, St. Luke's Hospital and Clinical Professor of Roentgenology, University of California Medical School. Pp. 269; 227 illustrations. Philadelphia: Lea & Febiger, 1936. Price, \$5.00.

THIS book fulfills its intended purpose; that is, "to meet the needs of the physician who wants to learn to interpret urograms, be he urologist, roentgenologist, general practitioner or interne." It is an excellent, compact and fairly complete treatise on roentgen diagnosis of urologic disease. It maintains the high standards of the previous writings of its authors.

The text, which is concise yet fairly comprehensive, includes a brief history of urography and a discussion of the necessary equipment as well as the technique for retrograde study of the urinary tract. Indications and contraindications for the retrograde and the intravenous methods of study are presented. A discussion of the roentgenologic appearance of the normal urinary tract is followed by chapters concerned with the Roentgen and clinical diagnosis of disease processes and anomalous conditions which affect the urinary tract.

Because of the extensive source of films and case histories, supplied by members of the American Urological Association, this book presents many unusual roentgenograms. The chapter on congenital anomalies of the kidney and ureter is particularly interesting from the standpoint of the more uncommon Roentgen appearances. The chapters concerned with the discussion of hydronephrosis, tuberculosis, stones and tumors are well planned and each preceded by an outline of its contents. A generous bibliography is included.

The physical properties of the book are such that it is easy to read. The paper is of good quality, the print large and sharp and the illustrations of the roentgenograms are unusually clear.

G. C.

DISEASES OF THE NAILS. By V. PARDO-CASTELLO, M.D., formerly Assistant Professor of Dermatology and Syphilology, University of Havana; Member of the American Dermatological Association, etc. With a Foreword by HOWARD FOX, M.D., Professor of Dermatology and Syphilology, New York University, University and Bellevue Hospital Medical College. Pp. 177; 94 illustrations. Springfield, Ill.: Charles C Thomas, 1936. Price, \$3.50.

A SEARCHING monograph on diseases of the nails, like many another monographic study of obscure items in dermatology, is badly needed. This brief work is unquestionably affected by the relatively small amount of research heretofore devoted to minor but nonetheless essential appendages of the human skin. The work therefore follows the conventional anatomical, pathologic and clinical classificatory lines, and probably perforce gives relatively little attention to function. It is an admirable descriptive catalogue, reinforced by really superb photography, and should enable the practising skin specialist to attach a name to practically any named condition of the nails now recognized. To this extent, also, it will serve the general practitioner and diagnostician, inasmuch as it illustrates the nail involvement associated with a variety of systemic conditions.

In therapeutics the work is practically restricted in scope to irradiation therapy with Roentgen ray, an unfortunate state of affairs, as much a commentary upon a limited outlook in the field of dermatology as it is any fault of the author. It must be conceded, on the other hand, that at least for temporary, and in some cases lasting results, Roentgen therapy of nail conditions is practically the most effective sole or adjunct therapy that we have.

The bibliography is short, conditioned by the subject and the mode of approach; the index is satisfactory.

This work is a step in the right direction. It is to be hoped that it will be followed by longer steps made possible by improved knowledge of the terrain as well as a better definition of monographic objectives.

J. S.

CLASSIFICATION OF YEASTS AND YEAST-LIKE FUNGI. By C. VIRGINIA FISHER, Ph.D., on Fleischmann Grant for Mycological Investigation, and LLOYD ARNOLD, M.D., Professor of Bacteriology and Public Health. Pp. 92; 10 plates. Urbana, Ill.: University of Illinois Press, 1936. Price, \$1.00.

FIRST is taken up the history and classification (both morphologic and biochemical) of yeasts in general. In succeeding sections, yeast infections of special regions (vagina, mouth, gastro-intestinal tract, skin) are briefly treated. The authors' own work included studies of morphology, biochemical reactions, pathogenicity, antiserum production, agglutination tests and complement fixation. A survey of the flora of normal skin and mucosæ of 577 persons is the basis for a catalogue of the characters of *saccharomyces*, *cryptococcus* and *monilia* (*endomyces* were not met), as well as of some of the species. A useful plan for the identification of species was submitted as well as a key.

The studies were conducted under reliable auspices at the University of Illinois and appear to be careful and thorough. Probably the most important outcome was the opinion that a study of morphology and biochemical reactions can suffice for identification; agglutination tests, while dependable, are not necessary except with doubtful strains. *Monilia albicans* was not found on normal skin, but occurred in feces, in gastric contents, and in mucous membranes under normal conditions.

F. W.

BONES. A Study of the Development and Structure of the Vertebrate Skeleton. By P. D. F. MURRAY, M.A., D.Sc. Pp. 203; 45 illustrations. Cambridge: At the University Press; New York: The Macmillan Company, 1936. Price, \$2.50.

THE author presents some new ideas and unpublished experiments. The main part of the book is in the first four chapters, where the author discusses the embryonic and postembryonic development, together with the structure of the skeleton in relation to its many functions. The language is so well chosen and simple that even a layman would not be mystified with unnecessary technical terms. This characteristic makes the book of special value to the young student interested in this field. There are also excellent photographs and clear, understandable diagrams. The concluding chapters are devoted mainly to the mechanism of bony adaptations and the conclusions drawn from these facts. Dr. Murray plainly states that he does not attempt to cover the field in its entirety or to be definite and final in his viewpoint; he hopes that his studies will help throw some light on the rather obscure processes of bony development. T. O.

A TEXT-BOOK OF NEURO-ANATOMY. By ALBERT KUNTZ, Ph.D., M.D., Professor of Micro-anatomy in St. Louis University School of Medicine. Pp. 519; 307 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, \$6.00.

THIS greatly expanded second edition shows many changes and additions and gives a well-balanced account of the structure of the nervous system from several points of view. There are 4 new chapters. These deal with the evolution and comparative anatomy of the nervous system (I), myelination (VII), peripheral and central spinal conduction pathways (XI), and laboratory directions and clinical illustrations (XXVI). In the latter 14 clinical cases are briefly presented. At the end of each chapter a summary of the important points is given in a page or two. This addition will be welcomed by the student, and is of real value in crystallizing the subject. Over 100 illustrations have been added from many sources, and enhance the usefulness of the book. W. A.

NEW BOOKS.

Trauma and Disease. Edited by LEOPOLD BRAHDY, B.S., M.D., Physician in Charge of Industrial Diseases and Accidents in the Office of the Corporation Counsel of the City of New York, and SAMUEL KAHN, B.S., M.D., Medical Examiner in the Bureau of Workmen's Compensation of the Department of Labor, State of New York, New York City, with 25 Contributors. Pp. 613; illustrated. Philadelphia: Lea & Febiger, 1937. Price, \$7.50.

The Thyroid and Its Diseases. By J. H. MEANS, M.D., Jackson Professor of Clinical Medicine, Harvard University, and Chief of the Medical Services, Massachusetts General Hospital. Being an Account Based in Large Measure on the Experience Gained in the Thyroid Clinic of the Massachusetts General Hospital by 14 Physicians and Surgeons and Many Other Collaborators, Past and Present. Pp. 602; 73 illustrations. Philadelphia: J. B. Lippincott Company, 1937. Price, \$6.00.

Source Book of Orthopaedics. By EDGAR M. BICK, M.A., M.D., Adjunct Orthopaedic Surgeon, Hospital for Joint Diseases and Mt. Sinai Hospital; Attending Orthopaedic Surgeon, Lutheran Hospital, etc. Pp. 376. Baltimore: The Williams & Wilkins Company, 1937. Price, \$4.00.

- The Avitaminoses.* The Chemical, Clinical and Pathological Aspects of the Vitamin Deficiency Diseases. By WALTER H. EDDY, PH.D., Professor of Physiological Chemistry, Teachers College, Columbia University, etc., and GILBERT DALLDORF, M.D., Pathologist to the Grasslands and Northern Westchester Hospitals, Westchester County, N. Y. Pp. 338; 3 illustrations and 27 plates. Baltimore: The Williams & Wilkins Company, 1937. Price, \$4.50.
- Medical Urology.* By IRVIN S. KOLL, B.S., M.D., F.A.C.S., Attending Urologist, Michael Reese Hospital. Pp. 431; 92 illustrations, 6 colored plates. St. Louis: The C. V. Mosby Company, 1937. Price, \$5.00.
- Yoga. A Scientific Evaluation.* By KOVOOR T. BEHANAN, PH.D., Institute of Human Relations, Yale University. Pp. 270; illustrated. New York: The Macmillan Company, 1937. Price, \$2.50.
- The Spectacle of a Man.* By JOHN COIGNARD. Pp. 252. New York: William Morrow & Co., Inc., 1937. Price, \$2.50.
- Contributions to the Microscopic Anatomy of the Pancreas by Paul Langerhans, [Berlin, 1869].* Reprint of the German original with an English Translation and an Introductory Essay by H. MORRISON, M.D. Pp. 39; illustrated. Baltimore: The Johns Hopkins Press, 1937. Price, \$1.00.
- The Cardiac Glycosides.* A Series of Three Lectures Delivered in the College of The Pharmaceutical Society of Great Britain under the auspices of the University of London. By PROFESSOR ARTHUR STOLL, D.Sc., M.D. (HONORIS CAUSA), of Basle, Switzerland. Pp. 80; 24 illustrations (1 in color) and 11 tables. London: The Pharmaceutical Press, 1937.
- Why We Do It.* An Elementary Discussion of Human Conduct and Related Physiology. By EDWARD C. MASON, M.D., PH.D., F.A.C.P., Professor of Physiology, University of Oklahoma School of Medicine, Oklahoma City. Pp. 177; 5 figures. St. Louis: The C. V. Mosby Company, 1937. Price, \$1.50.
- A Summer Camp for Diabetic Children.* Pp. 27. *New York Diabetes Association Annual Report for 1936.* Pp. 16. New York: New York Tuberculosis and Health Association, Inc., 1936.
- Clinical Allergy.* Due to Foods, Inhalants, Contactants, Fungi, Bacteria and Other Causes. Manifestations, Diagnosis and Treatment. By ALBERT H. ROWE, M.S., M.D., Lecturer in Medicine in the University of California Medical School, San Francisco; Chief of the Clinic for Allergic Diseases of the Alameda County Health Center, Oakland, Calif., etc. Pp. 812. Philadelphia: Lea & Febiger, 1937. Price, \$8.50.
- Autopsy Diagnosis and Technique.* A Manual for Medical Students, Practitioners, Pathologists and Coroners' Physicians. By OTTO SAPHIR, M.D., Chairman, Nelson Morris Institute for Medical Research; Pathologist, Michael Reese Hospital; Associate Professor of Pathology, University of Illinois Medical School, Chicago. Foreword by LUDWIG HEKTOEN, M.D. Pp. 342; 65 illustrations. New York: Paul B. Hoeber, Inc., 1937. Price, \$5.00.
- A Hundred Years of Medicine.* By WYNNDHAM E. B. LLOYD, M.A. (CANTAB.), M.R.C.S. (ENG.), D.P.H. (ENG.). Pp. 344. London: Gerald Duckworth & Co., Ltd., 1936. Price, 15/-.
- The 1936 Year Book of General Medicine.* Edited by GEORGE F. DICK, M.D., LAWRAON BROWN, M.D., GEORGE R. MINOT, M.D., S.D., F.R.C.P. (HON.) EDIN., WILLIAM B. CASTLE, M.D., AM., M.D. (HON.) Utrecht, WILLIAM D. STROUD, M.D., GEORGE B. EUSTERMAN, M.D. Pp. 848; 178 illustrations. Chicago: The Year Book Publishers, Inc., 1936. Price, \$3.00.

Hemophilia. Clinical and Genetic Aspects. (Illinois Medical and Dental Monographs, Vol. I, No. 4). By CARROLL LA FLEUR BIRCH, M.D., Assistant Professor of Medicine. Pp. 151; 23 plates of illustrations, 11 figures, 3 tables and 75 charts. Urbana, Ill.: University of Illinois, 1937. Price, Paper bound, \$2.00; Cloth bound, \$2.50.

NEW EDITIONS.

Physiology in Health and Disease. By CARL J. WIGGERS, M.D., Professor of Physiology in the School of Medicine of Western Reserve University, Cleveland, Ohio. Pp. 1124; 191 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1937. Price, \$9.00.

Synopsis of Pediatrics. By JOHN ZAHORSKY, A.B., M.D., F.A.C.P., Professor of Pediatrics and Director of the Department of Pediatrics, St. Louis University School of Medicine, and Pediatrician-in-Chief to the St. Mary's Group of Hospitals, etc. Assisted by T. S. ZAHORSKY, B.S., M.D., Instructor in Pediatrics, St. Louis University School of Medicine and Assistant Pediatrician to the St. Mary's Group of Hospitals. Pp. 367; 80 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1937. Price, \$4.00.

A Laboratory Manual of Physiological Chemistry. By D. WRIGHT WILSON, Benjamin Rush Professor of Physiological Chemistry, University of Pennsylvania. Pp. 288. Third edition. Baltimore: The Williams & Wilkins Company, 1937. Price, \$2.50.

"This laboratory manual of physiological chemistry is arranged for students familiar with elementary inorganic, theoretical and organic chemistry. It is intended to be used as a teaching manual and not as a comprehensive reference book. . . . As there is little variation in the type of material presented in various courses of physiological chemistry, we have found no difficulty in using this manual in our medical, dental and veterinary courses." (From Preface.)

A Medical Formulary. By E. QUIN THORNTON, M.D., Emeritus Professor of Therapeutics in the Jefferson Medical College, Philadelphia. Pp. 363. Fourteenth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1937. Price, \$2.75.

"The United States Pharmacopœia which became official July 1, 1936, shows drastic revisions to which this edition conforms. Twenty-eight modern drugs, preparations and chemicals have been added to the list of official substances and thirty-five official Latin names and forty-six English titles have been changed." (From Author's Preface.)

The Essentials of Chemical Physiology. For the Use of Students. By the late W. D. HALLIBURTON, M.D., LL.D., F.R.S., Fellow of The Royal College of Physicians; Emeritus Professor of Physiology in King's College, London, J. A. HEWITT, Ph.D., D.Sc., Senior Lecturer in Physiology, University of London, King's College, and W. ROBSON, Ph.D., D.Sc., Reader in Biochemistry, University of London, King's College. Pp. 350; 56 illustrations, including 1 colored plate. Thirteenth edition. New York: Longmans, Green & Co., 1936. Price, \$4.00.

The present edition, the first published after death of the original author, stresses the applications of biochemistry to physiology. It contains more didactic and explanatory matter than usually found but in works of this type the inclusion of discussions preserves the manual's readability. D. D.

Handbook of Microscopical Technique. For Workers in Animal and Plant Tissues. Edited by C. E. McCLEUNG, Ph.D., Professor of Zoology, and Director, Zoological Laboratory, University of Pennsylvania. Thirty-four Contributors. Pp. 698; 82 illustrations. Second edition, revised and enlarged. New York: Paul B. Hoeber, Inc., 1937. Price, \$8.00.

PROGRESS OF MEDICAL SCIENCE

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF
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MEDICINAL THERAPY IN PSYCHIATRIC DISORDERS.

I. THE HEMATOPORPHYRIN TREATMENT OF DEPRESSIVE PSYCHOSES.

IN the past few years several drugs of considerable interest have been introduced in the therapy of the psychoses. To name only a few, the treatment of morphine withdrawal symptoms with insulin, the use of insulin shock in the schizophrenic reactions, and the administration of benzedrine in affective disorders have been, and are at the present time, the object of intensive study. An historical survey of previous attempts to treat mental disorders by means of drugs must make even the most optimistic physician cautious in accepting enthusiastic reports without detailed and critical evaluation over a long period of time. Nevertheless, continuous therapeutic experimentation is indispensable in those psychiatric conditions in which our knowledge of etiology and our present methods of treatment are unsatisfactory. Although the study of the psychodynamics and psychologic mechanisms in the psychoses remains the focal point of interest for the psychiatrist, we welcome any method which may help us in treatment and at the same time may eventually clarify obscure etiologic problems. In the following, an important recent contribution in this field, the hematoporphyrin therapy of the depressions, will be reviewed.

The treatment of depressive psychoses with hematoporphyrin was inaugurated in 1930 by Hühnerfeld,^{17b,c} following a series of animal experiments,^{17a} in which he found that injections of small amounts of the substance resulted in gain of weight, overactive and aggressive behavior and increased response to external stimuli. Since depressions are characterized among other things by loss of weight, decreased psychomotor activity and lessened response to stimuli, Hühnerfeld regarded the drug as worthy of trial in human beings. By 1931 he was

able to report the results of treatment in 13 cases,^{17c} of which 11 had shown marked improvement or recovery, while only two were unchanged. A series of publications by this author continued to report highly favorable results.^{17d-j} By the end of 1935 Hühnerfeld had treated 90 cases of endogenous depression and involutional melancholia, all of them severe enough to require hospitalization; of these 48 recovered or were greatly improved, 30 were somewhat improved, and 12 were unaffected. The author believes that the consistently observed mode of recovery excludes the possibility of his having confused therapeutic effect with spontaneous improvement. The cases which responded to treatment showed, uniformly, first an improvement in the somatic-vegetative field (weight, turgor, sleep, etc.), and then a lessening of the mental symptoms, of which generalized inhibition (retardation) was usually the first to disappear. Moreover, clinical improvement in most cases was noted within 2 to 14 days after the treatment was instituted.

The treatment method, as recommended by Hühnerfeld, is of two types, oral and intramuscular. In mild cases the patient is given 10 drops of a 0.5% hematoporphyrin hydrochloride solution (oral "Photodyn") in water 3 times daily before meals. The dose is increased daily by 1 drop until it reaches 30 drops t.i.d., and then decreased at the same rate until the original level is reached, and treatment discontinued. Thus the usual duration of this type of treatment is 41 days, the total dosage somewhat less than 600 mg. In some cases the treatment is prolonged to 60 days with a dosage of 700 mg. When the psychosis is more severe, a 0.2% solution is injected intramuscularly, beginning with either $\frac{1}{2}$ cc. or 1 cc., followed by 9 injections of 1 cc. every other day. After the tenth injection a rest period of 7 to 10 days is interposed, after which a series of 10 injections of 2 cc. on alternate days is given; the first of these is frequently reduced to 1 cc. This type of medication lasts 47 to 50 days, with a total dosage of 57 to 60 mg. It has subsequently been modified by Hühnerfeld, who in his latest publications^{17i,j} recommends oral administration for mild and moderately severe forms of depression, and a combined oral and injection therapy for the very severe cases. In this latter method the patient is given small oral doses of hematoporphyrin, about 10 drops t.i.d., during the whole course of intramuscular injections, including the rest period, and thus receives about 300 mg. *per os* in addition to the 60 mg. injected.

The favorable results reported by Hühnerfeld soon led other clinicians to investigate the value of the method. In Germany, Italy, and France publications by André,² Becker,⁶ Bianchini,⁷ Cimbali,¹⁰ Gielm,^{12a} Hartmann and Weissmann,¹⁵ Küppers,²² Meyer,²⁷ Vinchon⁴¹ and others reported results which, although in general not quite as favorable as those of Hühnerfeld, nevertheless indicated that hematoporphyrin was of marked therapeutic value in a large number of depressions. In this country Strecker, Palmer and Braceland^{29a} were the first to undertake a study of this treatment, reporting in 1934 a series of 37 cases, of which 23 were manic-depressives, 8 involutional melancholias, and 6 schizophrenics. Excluding the latter, of the 31 depressives treated, 9 showed marked sustained clinical improvement, 7 moderate clinical improvement, 8 general physical improvement, while 7 remained unchanged. Their conclusions were that hematoporphyrin in some way

increases the available energy, and that actual somatic and psychic benefits seemed to be derived from its administration, especially in the affective disorders. In a second communication,^{39b} the same authors report equally favorable results in 24 additional cases. Angus³ administered hematoporphyrin to 41 cases of symptomatic depression of long standing, with an apparently poor natural prognosis. Included in this group were 15 manic-depressives, 11 involutional melancholias, 9 depressed schizophrenics, 3 depressed psychoneurotics, and 3 miscellaneous depressed states. Six of the manic-depressives improved greatly or recovered, 2 improved, 1 showed transitory improvement, and 6 were unchanged. The corresponding figures for the total group were 8, 10, 5 and 18. The author concludes that hematoporphyrin is of definite value in the treatment of depressions, including those of apparently malignant character. Most of the above mentioned authors agree with Hühnerfeld that it is possible to distinguish between the therapeutic effect of the drug and spontaneous improvement. Strecker, Palmer and Braceland list separately those cases in which they feel certain that the improvement was dependent upon the administration of hematoporphyrin, those in which this was highly probable but not certain, and those in which the evidence did not permit of a verdict one way or the other.

In contrast to the otherwise unanimously favorable opinion of those who have investigated the method, two publications report negative, or almost negative, results. Notkin *et al.*²⁹ treated 10 cases of involutional melancholia. One patient showed sustained improvement, 3 were moderately but only transiently improved, while the remaining 6 were unchanged. The same authors also experimented with hematoporphyrin therapy in 10 cases of schizophrenia, only 2 of which showed some depressive coloring; none of these patients improved. Steinberg³⁷ reported the results of treatment in 14 patients, comprising 8 manic-depressives, 5 involutional melancholias, and 1 undiagnosed psychosis. One manic-depressive showed sustained improvement, and another transient improvement; the remaining patients were not benefited. Hühnerfeld,^{17c,j} commenting on Steinberg's results, states that in addition to the diagnostic uncertainty of some of the cases he regards the doses used as too small for such severe depressions. It is true that where combined oral and intramuscular administration was used by Steinberg, the patients received on the average only 100 to 150 mg. of hematoporphyrin by mouth in addition to the 60 mg. by injection; but it is hardly likely, in view of the immediate improvement with corresponding doses noted by other observers, that this alone would account for the negative results. On the other hand, some of the cases were unquestionably diagnostically uncertain, and, what is more important, the series was a small one.

The total results of hematoporphyrin therapy to date can be summarized as follows, taking into account only those publications which list the number of patients treated, and the degree of improvement noted: Of 423 patients treated, 351 belonged to the group of endogenous depressions and involutional melancholias; of these, 173 (49.3%) recovered or were greatly improved, 103 (29.4%) were moderately or slightly improved, and 75 (21.3%) were not helped at all. Of the 71 cases of involutional melancholia, slightly more than $\frac{1}{3}$ failed to respond

to the treatment. Hühnerfeld, Giehm and Vinchon have observed that cases in which anxiety is a prominent feature are especially resistive to treatment. Hühnerfeld feels that exogenously conditioned (reactive) depressions are not amenable to this form of therapy unless endogenous factors also are present; and, in common with Schwarz, stresses the need for differential diagnostic studies in order to obtain more precise indications for the treatment. Angus³ believes that the main indication for the use of hematoporphyrin lies in the presence of symptomatic depression rather than in the minute diagnosis. Pending further large scale investigations, the evidence at present is greatly in favor of the assumption that hematoporphyrin exerts a markedly beneficial effect on many depressive patients, particularly in the endogenous (manic-depressive) group.

The dangers involved in the treatment appear to be minimal. Hühnerfeld considers it certain, on the basis of his experimental and clinical studies, that the doses recommended by him exclude the possibility of any serious toxic manifestations. Hutschenreuter¹⁸ found that 20 times the maximal oral dose used in treatment was well tolerated by rats, although postmortem microscopic examinations revealed fatty degeneration of the liver, hyperemia of the splenic pulp, and some hemosiderosis. The usual intramuscular dose produced some toxic effects, but in his opinion the difference in body weight between human beings and the experimental animals should allow for a wide margin of safety. To date no deleterious toxic effects have been noted, with the exception of a few unpleasant but harmless erythemas (Strecker *et al.*,^{39a} Tieke,⁴⁰) and 1 case of photophobia (Strecker *et al.*); one of the erythemas reported by Strecker *et al.* resulted from a nurse injecting the drug subcutaneously instead of intramuscularly. Steinberg³⁷ felt that in some of his cases the drug was definitely harmful from the psychiatric point of view, but noted no injurious toxic reactions. As regards somatic contraindications, Hühnerfeld limits these to organic affections of the liver and severe acute febrile disease. He has treated patients with pulmonary tuberculosis, nephrosis, arteriosclerosis and myodegeneration of the heart, and has observed no harmful effects. In all cases of organic illness, however, he restricts himself to the oral administration of the drug, and in very advanced arteriosclerosis reduces the dose to half the usual amount.

The encouraging results reported above, and the possibility that through further study of the method something may be learned as to an underlying metabolic disturbance accompanying or causing true endogenous depressions, have naturally aroused great interest in the mode of action of hematoporphyrin in these conditions.

The chemistry and physiology of the porphyrins can be discussed only briefly in this review. For an excellent presentation of the rôle of these substances in human pathology the reader is referred to Mason, Courville and Ziskind,²⁴ where he will find the literature cited in detail. Of even greater importance is the general biologic significance of the porphyrins, particularly as regards their chemistry, in which field great advances have recently been made. They are widely distributed in the plant and animal kingdom, being closely related to many of the major biologic pigments. Hematoporphyrin is derived from hemin (acid heme) by the splitting off of iron; heme being one of the two com-

ponents of hemoglobin. Phylloporphyrin, a magnesium-free derivative of chlorophyll, and hematoporphyrin, an iron-free derivative of hemoglobin, can both be reduced to the same substance, hemopyrrol. Cytochrome, an intracellular pigment found in aërobic bacteria, yeast, higher plants, and animals, is a derivative of heme, being composed of three hemochromogen-like compounds, cytochrome a, b, and c. Cytochrome c, when subjected to HBr-glacial-acetic-acid degradation, yields a crystalline hematoporphyrin. Egg-shells contain oöporphyrin, an isomer of protoporphyrin, traces of which are found normally in all human organs, in the feathers of some birds, in the sprouts of plants and elsewhere. The yeast cell can synthesize coproporphyrin, found physiologically in small quantities in feces, urine, milk, bile and meconium, and pathologically in larger amounts in the serum, urine and feces of individuals with congenital hematoporphyrin, as well as in plumbism, pernicious anemia and other diseases. Uroporphyrin is also found physiologically in normal urine, and in large amounts in all types of hematoporphyrin. The copper salt of this compound, turacin, has been isolated from the feathers of the turaco, a South African bird. These examples should suffice to illustrate the prevalence of these substances, and their importance in animal and plant physiology. Nevertheless, the assumption of earlier workers that hematoporphyrin was synthesized in the liver, and took part in the formation of hemoglobin, has not been substantiated by subsequent investigations, which have failed to produce any evidence that hematoporphyrin occurs in normal intermediary metabolism. The porphyrins found in the urine of healthy individuals as well as those seen in cases of so-called "hematoporphyrin" (better "porphyria") are uroporphyrin, coproporphyrin, and occasionally other natural porphyrins, but not hematoporphyrin. Recent experiments to determine whether orally or parenterally administered hematoporphyrin is partly converted into one or more of the natural porphyrins were inconclusive, but pointed to a negative result (Hutschenreuter¹⁸). Structurally, the various porphyrins differ from one another chiefly in the number of carboxyl groups in the molecule. Through decarboxylation of any of them, etioporphyrin, consisting of four substituted pyrrol rings, may be obtained. Although all the known porphyrins and many of their isomers have been synthesized, some question as to their structural formulas still exists. Hematoporphyrin, which contains two carboxyl and two hydroxyl groups, has the formula $C_{34}H_{38}O_6N_4$, but recent studies indicate that there may be only 33 carbon atoms instead of 34.

Two physicochemical properties common to all the porphyrins are fluorescence and the production of photosensitivity, which are closely related to one another. Photosensitivity in man was first described by Bazin⁵ in discussing the pathogenesis of hydroa vacciniforme. Anderson¹ reported the presence of porphyrins in the urine of patients with hydroa aestivale. The first actual demonstration of the photodynamic action of a drug, however, was made by Raab³³ in 1898, when he found that acridine solutions would kill paramacia much more quickly when exposed to light, although light alone had no deleterious effect on the organisms. Following this discovery much work was done on the phenomenon of photodynamic action, which has retained the interest of investigators up to the present time. For a discussion of the

nature of the photochemical processes involved, the reader is referred to the publications of Blum.⁸

The investigation of the photosensitizing effects of the porphyrins, particularly of hematoporphyrin, was undertaken by Hausmann.¹⁶ This author first proved that a strong solution of hematoporphyrin was fatal to paramecia, and demonstrated that under corresponding conditions erythrocytes were destroyed. He studied the effects of graduated doses of the drug on white mice, distinguishing four degrees of photosensitization according to the dose given and the intensity of irradiation. 1, In *light stroke* the animal first becomes restless, scratching the ears, nose, and other parts of the body violently. The pulse and respiration rate increase, and the skin becomes livid. Then the animal becomes comatose, the blood pressure falls, and death occurs. 2, In the *acute photodynamic reaction* the blood pressure first rises, accompanied by tachycardia and paroxysmal hyperpnea. A pronounced erythema appears over the entire body. Later the blood pressure falls rapidly, and the animal dies unless protected from light. 3, In *subacute photosensitivity* only erythema and edema of the skin are found. 4, In *chronic photosensitivity*, when the dose is still smaller, and the exposure to light brief but repeated, the animal's ears become necrotic, and hair falls out in a ring-shaped area around the eyes. These experiments have been repeated and expanded by various investigators in the attempt to explain the symptoms found. Pfeiffer³¹ performed an interesting experiment on parabiotic white rats, in which only one of the pair was exposed to light, but the other died subsequent to the irradiation, frequently before the irradiated partner. Smetana,²⁵ however, in a similar experiment with parabiotic mice found that only the one exposed to light was injured. Rask and Howell,³⁴ working with dogs, concluded that death was caused by vascular collapse, and demonstrated that the low blood pressure was due to paralysis of the cutaneous circulation and not to a toxic effect of the drug or of skin toxins on the central nervous system. Awoki⁴ found that white mice sensitized with hematoporphyrin and then narcotized with urethane did not show the usual motor excitation, but nevertheless died in the same length of time as unnarcotized mice when irradiated. This same author showed that serum injections will protect white mice against the fatal effects of hematoporphyrin sensitization. The experiments of Hühnerfeld and Hutschenreuter with small doses of the drug have already been mentioned. Strecker, Palmer and Braceland³⁹⁵ studied the behavior of white rats following graded intraperitoneal injections of photodyn. the commercial hematoporphyrin used in the treatment of depressions. Rat 1, used as a control, received no hematoporphyrin, but was exposed to ultraviolet radiation, during which he appeared much more active and interested; 30 minutes later he was active, eating and drinking; after 12 hours his behavior was normal. Rat 2 received 0.6 mg. of hematoporphyrin. Before exposure to ultraviolet light his behavior was normal; during exposure he was markedly hyperactive, and was even more active 30 minutes later, scratching himself, washing his face frequently, and apparently suffering from some irritation of the skin; 12 hours later he appeared normal. Rat 3, receiving 1.2 mg., was unchanged before irradiation, but during exposure appeared ill, was uninterested, and showed photophobia; after 30 minutes he was more

active than 1 or 2, and suffered marked skin irritation; 12 hours later he was still overstimulated, racing about. Rat 4 was given 1.8 mg. and showed no change before exposure to ultraviolet irradiation; during exposure he seemed definitely ill, with marked photophobia, sluggishness and inactivity; 30 minutes later he still was inactive and suffering from photophobia; after 12 hours he was extremely active and overstimulated, racing about his cage and climbing up the wire; the irritation of the skin was still present.

There have been comparatively few experimental investigations of the photodynamic action of hematoporphyrin in human beings. Meyer-Betz²⁸ experimented on himself with an intravenous injection of 0.2 gm., and suffered for weeks with extreme dermal photosensitivity. He observed that light which passed through a window pane was apparently no less injurious than direct sunlight. Strauch³⁸ administered 0.12 gm. intravenously to 3 rachitic children; all of them developed erythema and edema of the skin with subsequent ulceration and necrosis. Duke¹² showed that intradermal injections of small amounts of porphyrin caused local dermal sensitivity to light. Blum, in a personal communication to Strecker, Palmer and Braceland^{39b} reports the results of interdermal injections of photodyn in humans. The injection of 0.1 cc. of a 0.01% solution (0.01 mg.), followed by exposure to bright sunlight for 2 or 3 minutes, resulted in the formation of an extensive itching wheal surrounded by spreading erythema. The wheal subsided after 1 to 2 hours, and was succeeded later by pigmentation. Of particular interest was the fact that the removal of oxygen from the tissue by occlusion of the circulation prevented the formation of the wheal and the erythema. With a 0.004% solution it was very difficult to obtain any definite photosensitizing effect. Ohta³⁰ undertook studies of the blood and urine of hematoporphyrinized rabbits, using medium sized doses. The animals who were exposed to sunlight showed a decrease in hemoglobin and the number of erythrocytes, and an increase in fats and fibrinogen. Within the limits of the experiment no definite changes in blood sugar, carbon dioxide, total nitrogen and non-protein nitrogen could be elicited. A second group of animals, who were also given hematoporphyrin but were kept in the dark for a week, showed no appreciable blood changes. The urine was examined before and after sensitization; the values for creatinine, uric acid, urea, ammonia, total nitrogen, chlorides, calcium and magnesium were found to be unaffected.

Studies to determine the relative powers of photosensitization of the various porphyrins have been carried out by Schumm,³⁵ Dankmeyer¹¹ and Grzeschiuchna¹⁴ among others, and have shown that the commonest porphyrins may be graded as to photodynamic potency in the following order: hematoporphyrin, uroporphyrin, deuteroporphyrin, coproporphyrin, and protoporphyrin, the first named having 20 times the photosensitizing effect of the last.

The question as to what type of light has the strongest effects on hematoporphyrin-sensitized organisms is of considerable theoretical interest (cf. Blum^{3b}), and may prove of practical importance in the therapy under discussion. In common with the natural porphyrins, hematoporphyrin shows maximal absorption in the visible region of the spectrum around 560 m μ (yellow light), with a second peak at about 400 m μ

(violet and long wave ultraviolet). Kögel²¹ recently studied the sensitivity of hematoporphyrin in the concentration used by Hühnerfeld, and found that it was sensitive to the whole of the visible spectrum as well as to some infra-red and ultraviolet rays, but chiefly to yellow light. He concluded that ultraviolet irradiation, such as has been used by the majority of workers, can be of no particular advantage in hematoporphyrin therapy.

Boyd⁹ has made an interesting study of hematoporphyrin from a different point of view. Following the observation of Howell that hematoporphyrin and light were capable of changing fibrinogen into a more soluble form of protein, Boyd investigated this phenomenon to discover whether actual hydrolysis of the protein took place, and whether the reaction could be considered an enzymatic one. He found that four factors were necessary for the hydrolytic reaction: molecular oxygen, hematoporphyrin, water, and radiant energy. His theory of what actually takes place in this process may be summarized as follows: Hematoporphyrin unites with the protein in a salt compound. Through the absorption of light the energy of the hematoporphyrin molecule is increased. Molecular oxygen then unites with the hematoporphyrin molecule, and oxidizes it. Through this the energy content of the hematoporphyrin is increased to the point that it becomes unstable and decomposes, at the same time giving some of its energy to the protein with which it is united. The energized protein molecule then unites with water, and is hydrolyzed.

If, after this necessarily brief survey of the chemical, physical and biologic aspects of hematoporphyrin, we return to the question of how the drug acts when therapeutically administered to depressed patients, we find no explanation that is entirely satisfactory. Hühnerfeld's original hypothesis was that through skin sensitization stimuli were transmitted to the vegetative centers, thus exerting a favorable action in the "volitional and sensory spheres." In his more recent papers^{17,18} he distinguishes 3 modes of action of hematoporphyrin: 1, a photodynamic effect on the vegetative centers; 2, a stimulative- tonic effect, manifested by improved appetite, increased weight, increased turgor of the skin, and, where secondary anemia is present, an improvement in the blood picture; and 3, a vegetative-regulatory effect, as shown by increased salivation, lessening of gastro-intestinal and vasomotor disturbances, and by the reported influence of the drug on the electrolyte balance, on the blood-sugar level, and on the hydrogen-ion concentration of the urine. The theory of the transmission of stimuli from the photosensitized skin to vegetative centers, with a resultant release of inhibitions, is, as Hühnerfeld himself points out, merely a working hypothesis. As such it is accepted by the majority of European workers in this field, but it is wholly without experimental foundation, and at the present is not capable of being either proven or disproven. The laboratory data concerned with the postulated stimulative-tonic and vegetative-regulatory effects of hematoporphyrin will be reviewed below.

Boyd, in a personal communication to Strecker *et al.*,²² mentions two possibilities as to the action of hematoporphyrin. He quotes Zeile and Hellstrom to the effect that liver catalase contains an iron-porphyrin complex, and points out that cytochrome is known to contain

hemin. In view of these facts he suggests that hematoporphyrin may act as a respiratory catalyst, promoting a greater cellular respiration. Boyd's second theory, based on his investigation quoted above, is that following the reaction of hematoporphyrin with tissue proteins, highly reactive chemical substances may be split off, thus producing a stimulating effect on the organism, possibly in the form of a mild anaphylactic shock. Blum, in another personal communication to Strecker, Palmer and Braceland,^{39b} suggests that increased cellular respiration may be one of the major factors at work, and cites the demonstration by Wohlgemuth and Szörenyi that the oxygen intake of cells is increased by hematoporphyrin even in the dark, and to a much greater extent when light is present. It should be pointed out, however, that Wohlgemuth and Szörenyi⁴² believe this increased use of oxygen to be quite different from ordinary cellular respiration, in that it is dependent neither upon the structure of the cell nor to a great degree upon temperature. The theories of increased cellular respiration and of protein shock rest on a firmer experimental foundation than does Hühnerfeld's hypothesis of the transmission of stimuli to the vegetative nervous system through skin sensitization; yet both need further clarification before they can be accepted as even partial solutions of the problem. There can be no doubt but that the concept that hematoporphyrin plus light increases cellular respiration is of fundamental importance for further research in this field. Strecker, Palmer and Braceland suggest the possibility that this action may account directly for the therapeutic effect, citing the work of McFarland²⁵ on the psychological effects of oxygen deprivation; but it must be said that in general anoxemia results in toxic-delirious and occasionally schizophrenic-like symptoms, rather than in depressive ones. As regards the direct therapeutic effect of protein shock, there is no reliable clinical or experimental evidence that endogenous depressions are greatly influenced by shock effects; on the contrary, these conditions are characterized by a course which, more than in any other psychosis, appears to be independent of accidental somatic or mental stimuli, such as intercurrent febrile disease and psychic traumata. Only a few examples to the contrary are reported in the literature (Pilcz³²). Menninger²⁶ stated that only 2 cases of postinfluenzal recovery from depression were recorded in the literature up to 1930; Levin²³ has recently reported another. Furthermore, the clinical and laboratory data to date present no evidence that an anaphylactic-like shock, even a mild one, occurs in the usual course of treatment. Nevertheless, it would be worth while to test this theory by a carefully controlled series of depressives treated with protein shock therapy. As far as is known to the reviewer, foreign protein shock is one of the few forms of medication that has not, at one time or another, been tried in depressions. Autohemotherapy was recently studied by Giehm,^{13b} who obtained good results in reactive depressions (probably suggestive), but very poor ones in the endogenous group.

The data relative to the "stimulative-tonic" and "vegetative-regulatory" effects of hematoporphyrin can be summarized as follows:

Body Weight. Hühnerfeld^{17a} observed that 3 pigs, when given oral doses of hematoporphyrin in amounts which corresponded ac-

cording to weight with the usual treatment doses in humans, gained 40 to 50 pounds more than other pigs from the same litter, although receiving the usual nourishment. Clinically, he finds that in most cases the body weight increases, often rapidly, but gives no further information. Of the 37 patients treated by Strecker, Palmer and Braceland in their first series, 20 gained in weight, the average increase being $5\frac{1}{2}$ pounds, 10 patients lost weight, 3 of them being under weight reducing programs; and 7 patients showed no change in weight at the end of the treatment, although several of these had gained considerably at some time during the treatment. Angus³ found no appreciable change in those cases which improved, but a moderate gain in weight in the unimproved cases. Of the 20 patients treated by Notkin *et al.*,²⁹ 12 showed a gain in weight, and 8 a loss. The 3 cases which were temporarily improved gained, whereas the patient with sustained improvement lost 6 pounds, which were later regained. Steinberg²⁷ reported gain in weight in 1 of his 14 patients, loss of weight in 1, and slight loss of weight in 2; in the other 10 cases no mention is made of gain or loss.

Basal Metabolism. Angus found that the basal metabolism in cases improving under hematoporphyrin therapy tended to rise, while in the unimproved cases there was a slight decrease. These findings, however, were based on averages for the two groups; the individual findings were not consistent enough to permit of any definite conclusion. Notkin *et al.* obtained basal metabolic readings in 14 cases before, during and after treatment; in 9 of these there was an increase during treatment, in 2 no change, in 3 a decrease. The findings after completion of the therapy were inconclusive. In 1 case of involutional melancholia showing temporary improvement there was a slight increase during and after treatment; in the other 2 temporarily improved cases, and in the 1 showing sustained improvement, no readings were obtained. Strecker *et al.*, in 12 cases, found no consistent pattern, and chiefly negligible changes.

Hemoglobin and Red Count. Hühnerfeld¹⁷⁶ found in an unstated number of patients that "there was an almost consistent marked increase in the red count and hemoglobin, particularly in cases with secondary anemia," and feels that this observation to a certain extent confirms the old and subsequently discarded theory that hematoporphyrin takes part in the formation of hemoglobin. In their first series, Strecker *et al.* examined the blood of 16 patients, of whom 9 showed substantial increases in red blood cell count and hemoglobin, 1 was unchanged, and 6 showed moderate reduction. In their second series the same authors found slightly higher erythrocyte counts (100,000 to 250,000) in 8 cases, and slightly decreased counts (30,000 to 70,000) in 2. These are scarcely beyond the limits of biologic and technical variation. The accompanying hemoglobin changes were negligible, as were the variations in the white cell count. In the remaining 2 cases of the 12 examined the changes were greater. One patient with a moderate secondary anemia (Case 11) showed an increase of 740,000 cells, combined with a marked rise in hemoglobin; the other (Case 4) showed a decrease of 740,000 with no marked change in hemoglobin. Steinberg found the erythrocyte count lowered in 4 of the 5 cases examined; in one of these the decrease amounted to 1,350,000 cells.

Notkin *et al.* found increases of from 150,000 to 1,500,000 cells in 15 of the 19 cases examined; the average increase was 643,000. Angus observed an increase in hemoglobin and red count in most of his improved cases, but noted that in the unimproved group a distinct fall in both factors was the rule rather than the exception, and raised the question whether this may in the future prove to be a danger point in the therapy. In view of repeated experimental evidence that large doses of hematoporphyrin followed by irradiation can cause hemolysis of the erythrocytes, this warning is timely, and should lead to regular and frequent counts on all patients undergoing treatment. Detailed hematologic investigations of the effect of varying amounts of hematoporphyrin on animals and humans would be of great interest. At present, it appears that the drug, in a majority of cases, increases the number of erythrocytes when administered in small doses; the effect on the hemoglobin content is much less certain.

Blood Sugar. Küppers²² found that hematoporphyrin lowered the blood sugars of his patients, particularly when some hyperglycemia was present before treatment. Although various reports on high blood sugars in depressions have appeared to the literature, Katzenelbogen and Friedman-Buchman²⁰ have shown that in general the values in these conditions are within normal limits. These authors, however, in common with several other investigators, found that the *sugar tolerance curve* in depressions shows a higher peak and a more prolonged decrement than otherwise. In general, the curve becomes normal with recovery from the illness. Angus made careful studies on the effect of hematoporphyrin on the sugar-tolerance curves, with the following findings: 1, The blood sugar was within normal limits before and after treatment. 2, The blood sugar fell during treatment. 3, The sugar-tolerance curves became more normal after treatment, not only in the improved cases, but to a lesser degree in many of the unimproved ones. This latter finding seems particularly significant insofar as it demonstrates that hematoporphyrin, even in cases in which no clinical improvement is noted, can produce laboratory findings which are usually associated with recovery. Steinberg, who examined blood sugars before and after treatment, but not during it, found no consistent changes. His values before treatment were extremely low; in the only case with a sugar level above 100 (105.26), the reading after treatment was 79. The same author investigated the *blood cholesterol* of 6 patients, and found a decrease following treatment in all of them.

Electrolyte Balance. Irrespective of whether or not the blood calcium level in depressions is raised, as is claimed by many investigators, or within normal limits (Katzenelbogen and Goldsmith¹⁹), the question as to the action of hematoporphyrin on the calcium-potassium balance is of great interest. Hühnerfeld^{17c} found that hematoporphyrin reduced the calcium values in patients with hypercalcemia. Later,^{17d} in experiments with pigs, chosen because their blood calcium level is similar to that of humans, he was able through the administration of doses comparable to those used in hematoporphyrin therapy to reduce the blood calcium of the three animals by 2.5 to 3 mg. %. The calcium level was lowest at the time when the largest doses were given, and returned to normal 4 weeks after the medication was terminated. Küppers and Vinchon^{41a,c} confirmed these results clinically. The former

author in particular emphasized the importance of these findings, and expanded on them, claiming that in favorable cases the potassium level is raised concomitantly with the decrease in calcium and blood sugar, thus forming an important prognostic guide. Vinchon^{41b} mentions in connection with the electrolyte balance his observation that the pH of the urine is lowered by hematoporphyrin. In 1 patient studied by Strecker *et al.* in their first series, the calcium values were 11.8 and 11.5 mg. % before treatment, 9.6 mg. % during treatment, and 10 mg. % afterwards. In their second series, 12 patients were examined and showed on the whole a slight increase. No correlations with improvement were attempted. Angus found varying decreases in both improved and unimproved cases, somewhat larger in the former; exceptions occurred in both groups, however. Steinberg's series shows 5 decreases as against 2 increases, but some of the changes were negligible. In this connection a factor should be mentioned which has not been taken into account by any of the investigators, and which may well play a rôle in obscuring the experimental results. Ultraviolet light, which has been used in varying amounts by different workers with hematoporphyrin, can, through radiation of ergosterol with resultant vitamin D formation, raise the calcium level of the blood; accordingly, the effects of hematoporphyrin on blood calcium can be evaluated only in cases not exposed to large amounts of ultraviolet.

It is apparent that, whatever may be the final judgment as to the therapeutic efficacy of hematoporphyrin treatment, it offers at the present time an unusual opportunity for combined biochemical, general medical and psychiatric research. Further progress will, it is felt, depend to a large extent on the degree to which laboratory findings can be correlated with the results of careful and persistent clinical psychiatric examinations.

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OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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RECENT ADVANCES IN THE TONSILLAR ASPECTS OF SYSTEMIC DISORDERS.

THAT the tonsils continue to be a topic of interest to the otolaryngologist, as well as to the internist and general practitioner, is evidenced by the large number of contributions appearing upon the subject in recent years. While no spectacular discoveries that might profoundly affect our previous conceptions have been reported, there is a large number of interesting papers that serve to clarify our knowledge of tonsillar disease, especially as they relate to the complications incident to tonsillar infection and establishing more definite indications for their removal. There is an unmistakable trend away from the indiscriminate wholesale removal of the tonsils for various more or less vague reasons. Indications are becoming more precise and undoubtedly there is an increasing aversion from the so-called "slaughter of the innocents" unless the indication be placed upon a firm clinico-pathologic basis.

Pathology. That grossly pathologic tonsils which upon microscopic examination show varying evidence of chronic inflammation may frequently be attended with little or no clinical phenomena is a matter of common knowledge. Mueller³⁷ finds that the clinical and anatomic picture but rarely agree; many histologically pathologic tonsils manifesting few if any clinical symptoms. Even the purulent-appearing cryptic contents obtained by tonsillar expression are but rarely true pus; but, as Krompecher and Nemaï³⁰ find; are exfoliated epithelial

cells that have undergone fatty degeneration and have as an admixture a varying number of neutrophils, lymphocytes, plasma cells, macrophages and bacteria. Smith⁵⁷ compared the clinical history and the histopathologic findings in a group of 104 tonsillectomies. Of the 45 cases that were operated upon because of repeated sore throats and colds, 87% showed histologic evidence of chronic inflammation, while 13% were normal. Of the 17 patients operated upon because of discharging ears, 59% evidenced infection and 41% did not. Those operated upon because of a possible focus of infection showed microscopic evidence in 86%. In a similar attempt to correlate the relation of the pathologic picture of a tonsil with the clinical cause for its removal, Jason⁵⁸ found that patients with systemic or distant changes showed greater tonsillar changes than those with purely local pharyngeal complaints. Hunnicut, Sternstein and McMahon,²¹ in a study of 25 tonsillectomies, were unable to find any histologic change that was definitely related to either the clinical signs and symptoms or the bacterial flora. The pathologic findings were similar to those found in a control group. Even normal-appearing tonsillar fossæ may harbor infective organisms after tonsillectomy, is a conclusion of Solis-Cohen,⁵⁸ after finding the same pathogenic organism both before and after tonsillectomy. Should this be substantiated, the possible cause of many failures of improvement of systemic disorders following removal of the tonsils is obvious. In the study of the tonsils as a possible focus of infection in systemic disorders, Nissen^{43a} found that the gross lesions were of 4 types, namely, acutely inflamed tonsils with or without supuration; chronically, reddened hypertrophic tonsils with or without symptoms; a tonsil in which the anterior pillar or soft palate is purplish red in color, and the presence of infected pharyngeal follicles. Tilley⁶¹ also believes that a purplish-red discoloration of the anterior pillar signifies a pathologic tonsil, especially if the tonsillar gland is enlarged and there is an abundance of pus extruded from the tonsillar crypts that contain a preponderance of leukocytes upon microscopic examination.

Cardiac Disease. In consideration of the question of the optimal time for tonsillectomy in the presence of a complicating endocarditis, Zimányi⁶⁵ calls attention to the many untoward results that are encountered if the operation is performed at a time in which the defensive mechanism of the body is at low ebb. He believes that the patient is in an optimal condition for operation when his defensive mechanism is most efficient and in a positive phase that can be shown by determining the bacteriologic index which normally is between 50 and 55. Tonsillectomy should, therefore, be performed only at a time in which the bacteriologic index is normal in order to avert any possible disastrous complication. A bacteriologic index below normal should be a contra-indication to operation.

It is to be admitted that tonsillectomy is frequently of benefit in endocarditis; Curtius, Dieker and Wirth¹⁹ observed in 41 tonsillectomies that existing cardiac conditions frequently improve after the procedure, although an exacerbation may be noted if decompensation has been present. Of the 23 patients that survived to the reëxamination time, 13 showed disappearance of the cardiac symptoms. There was little, if any, benefit if the operation was performed in a period in which there

existed a febrile florid endocarditis, and the authors properly concluded that the operation should only be performed during an afebrile period. In 8 patients with an endocarditis lenta no effect on the fatal course was noted.

Holtz and Friedman¹⁹ described a red eruption on the oral and pharyngeal mucosa that occurred in association with cases of rheumatic endocarditis. They were small pinpoint to 2 mm. circular, crimson to bluish, non-elevated lesions. They appeared in recurring crops lasting about 24 hours. The authors believed the eruption to be a non-embolic hemorrhagic exanthem.

Rheumatic Fever. There has been continued interest in the relation between tonsillar disease and arthritis and rheumatic fever. Kaiser²⁵ finds that while sore throat was the preceding infection in 59% of his 1200 rheumatic children, the recurrent attacks were not lessened in tonsillectomized children. The mortality rate was 50% less in children who had their tonsils removed, and the incidence of rheumatic infection was slightly more in children whose tonsils were not removed at the initial attack. In a study of histologic serial sections of the neck organs, Sarafoff⁵¹ was unable to find any typical changes in the tonsils and adenoids in several cases of rheumatic fever. On the contrary, the peritonsillar tissues disclosed evidence of rheumatic disease in 4 of 7 cases. Evidence of non-specific infection were found throughout the pharynx, indicating that in all probability the tonsils were not the sole portal of entry. In similar studies, Klinge²⁷ found serial sections of the tonsils in 2 patients that revealed similar evidence of rheumatic infection in the peritonsillar structures. In 5 other patients with a similar history, no specific rheumatic findings in the peritonsillar tissues were noted. In a study of the blood in rheumatic patients that had acute streptococcic pharyngeal infection, Schlesinger and Signey⁵² could demonstrate the presence of streptococcic precipitins, which corresponded to the type of organism responsible for the infection. Their appearance usually foreshadowed an attack of acute rheumatism, and the authors believe that immediate therapy instituted promptly would prevent serious relapses, although they concede that it is not infallible.

In a discussion of the part played by the tonsils and adenoids in the etiology of rheumatic fever, Coates and Gordon⁸ emphasize the importance of lymphoid remains, hypertrophied lateral pharyngeal bands and isolated lymphoid follicles on the posterior pharyngeal wall.

Blood Dyscrasias. There appears to be further concern with the pharyngeal lesions associated with blood dyscrasias. Jones²⁴ properly points out that the presenting symptom in many blood dyscrasias is a marked throat manifestation that the patient not infrequently consults an otolaryngologist, who must be aware of such a possibility and be prepared to perform the ordinary simple laboratory tests in every suspected case. A description of the early pharyngeal lesions in 3 cases of agranulocytosis by Costen⁹ calls attention to the frequency with which the anterior pillars are involved. The lesions represent a necrotic process on the surface of the tonsil or a mere solution of the tissues involved. All 3 cases gave a history of prolonged drug ingestion which the author believes is evidence of the profound depression of the bone marrow function caused by certain medicaments. Larsen³² points out that some believe agranulocytosis to be a real clinical entity provoked

by some unknown factor, while others regard it as the expression of a disturbed leukopoietic system as a sequel of a general infection. Another theory is that the clinical findings are an expression of a state of low general resistance following a disturbance originating in the bone marrow. He describes his case as one of secondary development, caused by infection with toxic effects on the bone marrow. Gangrenous tonsillitis may be an expression of an acute lymphatic leukemia. Nagasawa⁴⁰ reports a case of a child of 4, who had a swelling and redness of one tonsil and the neighboring palate. The upper pole of the tonsil was necrotic; there was anemia and glandular swelling. Microscopic examination of the blood disclosed acute lymphatic leukemia, with death in 1 week. Richter⁴⁹ presented 2 cases of acute sore throat attended with a constant lymphocytosis, with a normal or slightly subnormal total number of leukocytes. The lymphocytosis persisted after the acute infection had subsided. He investigated several close members of the respective families and found a similar lymphocytosis present, and so concluded that the phenomenon was a constitutional and familial characteristic. The clinical aspects of infectious mononucleosis was presented by McKinley³⁴ in a study of 50 patients over a period of 12 years. He advocates the term "infectious mononucleosis" in order to avoid such nondescript terms as "glandular fever." The most constant feature was the cervical lymphadenopathy, which may persist for some time and does not suppurate. Marked glandular enlargement was observed in individuals with but minimal pharyngeal findings. Pharyngeal findings varied from slight faucial injection to swelling of the lymphoid tissue and infrequent membrane formation. There was a variable total leukocytosis up to 30,000. There was a relative and absolute lymphocytosis present at some time in the course of the disease. There were no characteristic bacteriologic findings in the pharynx and blood cultures were repeatedly negative. There was no demonstrable effect on the injection of emulsion of fresh glandular substance into guinea pigs and monkeys. It would appear that the constancy of the lymphadenopathy would suggest that the offending etiologic factor and the primary lesion reside in the lymph nodes. There has been further interest in the serologic diagnosis of infectious mononucleosis made by testing the blood serum for the presence of heterophilic antibodies. This new phase in the diagnosis of this disorder was initiated in 1932 by Paul and Bunnell⁴⁴ when they found that the blood serum in such patients was able to clump sheep red cells in high dilutions, which normally occurs only in decidedly low dilutions. Davidsohn and Walker¹² and Stuart and others³⁹ reported on the nature of the heterophilic antibodies found in infectious mononucleosis. Bernstein⁴ showed that this disorder may be simulated by some 29 conditions and that the value of the test is apparent, and Davidsohn^{11a} enumerates several others. In another contribution on the subject, Davidsohn^{11b} concludes that the test is of decided confirmatory value in typical cases, and of diagnostic importance in the differential diagnosis of conditions that may simulate it.

Nephritis. In an extensive review of the subject of the bacteriologic aspects of peritonsillar phlegmon, Guilfrida¹³ reports that a transitory albuminuria could be observed in 37% of all cases of peritonsillar suppuration, a true parenchymatous nephritis being observed in 2%. Of the 37% complicated by renal involvement, streptococci were the

offending organisms in 20 % and pneumococci in 13 %. In a discussion of the value of tonsillectomy in children, Nadoleczny³⁹ concludes that acute glomerular nephritis and embolic focal nephritis without nephrosclerosis are frequently improved by tonsillectomy, while chronic nephritis is unaffected by it. deWesselow, Goadby and Derry⁶⁵ investigated the urinary findings in 354 patients with tonsillitis. There was present an early albuminuria in some 15 % of the patients and a late albuminuria in 6 %. From the clinical and urinary findings a focal nephritis was probably present in 10 % and a diffuse glomerulo-nephritis in 0.8 %. There was apparently no relation to the presence of hemolytic streptococci in the pharynx and the incidence of the focal nephritis.

Arthritis. In a study of 500 patients with arthritis, Nissen^{43a} noted that 90 % had their tonsils intact before the onset of the joint symptoms. In addition to the usual pathologic tonsil, Nissen believes that infected lymphoid tissue in the nasopharynx is a greater focus of infection than is usually realized. In another contribution^{43b} he stresses the importance in determining three important factors that associate arthritis with tonsillar disease, namely, the recognition of obvious or concealed infection in nasopharyngeal tissue, recognition of the involvement of the joints and other systemic effects, and determination of the association between the two. These are carried out by careful, prolonged and intensive study of the patient. In a discourse on the treatment of 438 patients with rheumatism who had tonsillectomy performed, he found that 300 were entirely symptom free, 100 showed varying degrees of improvement and in 38 no benefit was noted.

Endocrines. An endocrine rôle has frequently been attributed to the tonsils. Peller⁴⁵ in a large statistical study, in comparing the state of the tonsils and the constitutional attributes, concludes that they act as inhibitors to growth, weight, height and rate. This action is apparently unaffected by the presence of chronic infection. He believes the tonsils to be definite endocrine organs. He finds that tonsillectomized girls menstruate and mature earlier than average girls. Blonde girls he finds present tonsillar hypertrophy and are consequently more often tonsillectomized than brunettes. He concludes that further research is necessary to explain these and other relationships. In another contribution in association with Zimmerman,⁴⁶ he finds that the tonsils inhibit puberal development of the mammary glands, as tonsillectomized girls show earlier mammary maturation. Halasz¹⁴ believes that the tonsils are endocrine glands and that a deficiency in their internal secretion aids in the formation of ozena. He states that this disagreeable affliction may be benefited by subcutaneous injection of tonsillar extract in addition to extracts of the closely related thymus and thyroid glands.

Pulmonary Suppuration. The question of post-tonsillectomic lung infection continues to receive interest. Waldapfel^{64a} is unable to explain the relatively large number of pulmonary complications seen in this country in comparison to the relatively infrequent reports from Germany. He believes that it might be due to the superficial anesthesia, retention of the pharyngeal reflexes and use of the upright position. In 8 cases of post-tonsillectomic pulmonary complications he found that fever and roentgenography were most important in arriving at a diagnosis. The prognosis in his cases was good. Schutz⁵⁵ describes the various pulmonary complications following tonsillectomy and finds

they are not serious as a rule and clear up quite rapidly. He reviews the theories of formation and finds that of aspiration is untenable, as it is practically impossible to produce pulmonary abscess in animals by injecting blood and pus into the bronchi. Injections of infected material into the jugular vein on the other hand produced septic pulmonary infarcts. As with most German writers, he attributes the large number of such complications reported in this country to the use of deep general anesthesia. Ranson and McGolrick,⁴⁸ in reporting a case that recovered following operation, briefly discussed the manner of production and the treatment.

Tuberculosis. In discussing the tonsil as a portal of entry in tuberculosis, Schlittler^{53b} reviews 98 cases of chronic cervical lymphadenopathy but in whom no evidence of tuberculosis of the lung or other portions of the body could be discovered. Histologic examination of the tonsils removed in these individuals disclosed tuberculosis in 48. Only one tonsil and consequently only one-sided cervical enlargement was noted in 73% of the cases. Schlittler believes that the localization of the lymphadenopathy to the glands at the angle of the jaw draining the tonsils, the absence of tuberculous disease in other portions of the body and the relative frequency of unilateral involvement and the discovery of microscopic evidence of tuberculosis in such a high percentage of the excised tonsil all speak for the tonsils being the seat of a primary tuberculosis. In another contribution on the subject,^{53a} he stresses the presence of a subacute and chronic lymphadenitis of the angle of the jaw as a diagnostic sign of primary tonsillar tuberculosis. In a study of 112 tuberculous adults, Newhart, Cohen and Van Winkle⁴² found tuberculous tonsils in 42%. They also find that the tuberculous lesion is rarely a gross one, only being found at microscopic examination. This is in agreement with Schlittler's findings noted above. In addition, it was observed that in some instances in which routine sections were reported as normal, serial sections revealed tuberculous foci. There were no primary lesions noted in their cases, all being secondary to the open pulmonary lesion and resulting from constant contact with the bacillus-laden sputum. They conclude that tonsillectomy presents no special hazard when proper precautions are taken in tuberculous individuals. Hudson and Wollaston²⁰ cite a case of massive tuberculosis of the tonsils which gave a history of repeated attacks of sore throat over a period of 2 years. They conclude from the clinical course and from the histopathologic findings in the tonsils that the primary focus of the tuberculous infection was in the tonsils.

Syphilis. Sore throat and tonsillitis are relatively common findings in early syphilis. These persist for some time with few constitutional symptoms. In a study of 803 patients with early secondary syphilis, Brittingham⁵ found subjective sore throat and objective tonsillitis in about 29%. Of 502 patients with secondary syphilis, tonsillar lesions were observed in about 25%. In 301 patients with ultra secondary disease, tonsillar changes were noted in some 35%. It is apparent that routine serologic tests must be employed in all cases of pharyngeal involvement without systemic manifestations that persist for more than a week. In a study of the tonsillar tissues of 139 syphilitic patients macerated and subjected to dark-field illumination, Kumazawa²¹ was able to find the spirochete in 3 of 13 patients with primary lesions and

in 18 of 27 patients with secondary lesions. In later stages of the disease the spirochete could be observed even in individuals in whom the Wassermann reaction was negative. Pund and Brawner⁴⁷ described the histopathologic findings in 2 cases of syphilitic tonsillitis. They were characterized by a diffuse fibroblastic and angioblastic proliferation with large mononuclear cells in the lymphatic stroma. There was, in addition, foci of epithelioid cells in the neighborhood of the crypts. Mainzer³⁵ reports 2 cases of syphilitis of the tonsil. Chancre of the tonsil is unilateral, as a rule coming on with a sore throat, enlargement of the tonsil, and eventually swelling of the regional lymph glands.

Tonsillogenic Septicemia. In a survey of tonsillogenic sepsis, Haymann¹⁶ found an incidence of 5.3 per 1000 in a review of 12,500 necropsy reports. In some 30 % of the cases the tonsils could not be grossly identified as the origin of the sepsis, and in about 35 % peritonsillar or retropharyngeal abscess was present. He suggested that the sepsis could originate by direct entrance of the causative organism into the blood stream, from isolated thromboses of the retrotonsillar veins, by indirect entrance *via* the lymphatic channels and by secondary venous thrombophlebitis from parapharyngeal phlegmon. Waldapfel^{64b} differentiates two types of sepsis: *via* retrograde thrombophlebitis and by means of the lymphatics and lymphadenitis and secondary involvement of the cervical vein. He also stresses the fact that the primary portal of entry, the tonsil, is not always the focus of sepsis which is most often in the parapharyngeal space, and that appropriate therapy must take this fact into account. He therefore opens the neck in every suspicious case in order to drain the parapharyngeal space and to examine the jugular vein. He also removes the tonsil if local gross changes are present. The clinical manifestations indicating such a procedure are symptoms of general sepsis, associated with chills and the finding of tenderness and infiltration along the course of the jugular vein. He stresses the jugular glands as septic foci and insists on their removal when inflamed. Beck² discusses the diagnosis and treatment of parapharyngeal infections and jugular thrombosis, emphasizing the tonsils as the point of origin and indicating surgical drainage of the neck and resection of the jugular vein. Uffenorde⁶³ reports several cases illustrating the pathway from the infected tonsils to the lymphatics and the lymph glands and then involvement of the jugular and facial veins. He advocated enucleation of the tonsils, opening of the vascular sheath in the neck, removal of the inflamed glands, inspection of the veins of the neck and their resection if thrombotic and opening of the parapharyngeal space. Myers³⁸ reports 3 cases of post-tonsillitic pyemia with septic metastases in various portions of the body. In a discussion of postanginal sepsis, Abt¹ reports 4 cases in children and stresses the grave prognosis. He concluded that the earlier the responsible focus is detected and evacuated the better the prognosis. The similarity of postanginal septicemia to puerperal sepsis is discussed by Schneider.⁵⁴ Both diseases spread by vascular, lymphatic and perivascular phlegmon routes. They both may eventuate into pyemia with secondary suppuration in the joints, kidneys, lung and heart. The therapy is comparable in both disturbances, the elimination of the primary locus, the evacuation of suppurative collections, the ligation and resection of veins in the presence of endophlebitic extension. Both are extremely

grave diseases with a fatal outlook in about 50%. Hybasek²² reports several cases of sepsis following angina and tonsillectomy and concludes that drainage in sepsis is more important than tonsillectomy. Peritonsillar abscesses should be evacuated and drained, but tonsillectomy is contraindicated in peritonsillar phlegmon. He believes that there is little need for prophylactic ligation of the jugular, but advises ligation and resection of all thrombotic vessels. There must be thorough incision and drainage of the neck and parapharyngeal space. In contradistinction to the occurrence of sepsis following tonsillitis, Krauspe²⁹ presents clinical and experimental evidence that tonsillitis may at times be a sequel to a blood stream infection. Histologic examination of the tonsils in a number of individuals who died of a variety of acute infections disclosed inflammatory reactions which were interpreted as being hematogenous in origin. There were many abscesses and focal areas of necrosis. Bacteria, especially the streptococcus, could be demonstrated in the subepithelial capillaries. Kolbe²³ was able to demonstrate hematogenous metastases in the tonsils in 1 of 16 cases of general sepsis. He believes that the tonsils are infrequently so affected as they appear to possess a certain immunity.

Scarlet Fever and Diphtheria. The effect of tonsillectomy on the development of immunity was studied by means of the Dick test by Kereszturi and Park,²⁶ who were unable to note any marked effect in changing a positive Dick reaction to a negative one. Buice⁶ subjected a number of children to the Schick test and found the proportion that gave a positive reaction to be about the same in both, namely 62% in tonsillectomized children and 69% in those with intact tonsils. In a comparison of the course of scarlet fever and diphtheria which occurred before and after tonsillectomy in several thousand cases, von Zsindely^{76b} found a decreased incidence of both after tonsillectomy, but also noted the decreased incidence declined with the elapsed time following operation. In another communication, von Zsindely^{70a} observed that the percentage of diphtheria carriers were higher in the presence of enlarged tonsils and adenoids.

The Question of Tonsillectomy for Peritonsillar Abscess in the Acute Stage. In the past decade there have been increasingly more contributions advocating the performance of tonsillectomy in the acute stage of a peritonsillar abscess. While many feel that such a procedure is without danger, there are many theoretical objections which are obvious and that may find support in practice. In a discussion of 90 patients upon whom tonsillectomy had been performed for peritonsillar abscess, Zollner^{79a} reports several complications including a temperature rise to 104.8° F. with chill, and also a phlegmonous infiltration in the base of the tongue. He notes that patients in whom only simple incision is performed had an immediate drop in temperature more often than those tonsillectomized, and that postoperative febrile episodes were more common in the tonsillectomized than in the incised patients. He concludes that incision is the procedure of choice in early peritonsillar abscess and in those cases in which the abscess is well localized. Tonsillectomy should be reserved for those cases in which no pus is obtained and in which fever persists after simple incision and when there are signs of sepsis. In another contribution^{79b} he reports 4 fatal cases in 91 patients tonsillectomized for peritonsillar abscess. All died of septi-

emia in spite of relatively good pre-operative conditions of the patients. He finds simple incision adequate in most cases and finds indication for tonsillectomy in the three states noted above, namely, delayed recovery following simple incision, failure to recover pus on incision, and in the presence of sepsis. In review of 356 cases of peritonsillar abscess including 29 of his own, Tato⁶⁰ concludes that tonsillectomy affords a quick, safe, cure, eliminating the possibility of recurrence. He had but two complications: a postoperative hemorrhage and 1 case of sepsis with rheumatism. Hofer and Motloch¹⁸ review 30 patients with peritonsillar abscess treated by tonsillectomy. They noted a prompt drop in the temperature with but one exception. They believe that tonsillectomy in this condition is free from danger and is the operation of choice. In a series of 542 patients with peritonsillar abscess, Tonndorf⁶² found that 99 % showed adequate relief by simple incision through the anterior pillar. He believes that while tonsillectomy is not as serious as might be expected, its indication is present only in sepsis and in which healing fails to occur after simple incision. A comparison of simple incision, incision and secondary tonsillectomy, and tonsillectomy in the acute stage of the disease by Linck,³³ causes him to conclude that simple incision at times does not evacuate all the pus and that recurrences and relapses are common. Incision and secondary tonsillectomy has the advantage that complications are avoided by the removal of the tonsil. However, the disadvantage of the multiple operation and the possibility that a recurrence or relapse might occur before the secondary operation, lead the author to conclude that immediate tonsillectomy is the operation of choice for both immediate cure and prophylaxis against future difficulty. Advantages that are claimed are that there is not peritonsillar collection of pus that cannot be evacuated by this method, recurrences are impossible as no abscess cavity can exist after tonsillectomy. The author minimizes the danger that might be expected in operating upon acutely inflamed tissue and upon decidedly sick patients. Canuyt⁷ has had experience with many tonsillectomies in peritonsillar abscess, but considers it painful and at times dangerous. Neither does he believe in waiting for long periods of time for removal of the tonsil until marked postinflammatory adhesions are formed which may make the future procedure difficult and also run the danger of a recurrence during the interval. He advocates waiting for a period of 4 or 5 days after the simple incision preferably after the temperature has dropped to normal or nearly normal. He believes that at this time the operation can be safely, easily performed under local anesthesia.

The Value of Surgical Diathermy in the Treatment of Chronic Tonsillitis. Surgical diathermy or the use of electrocoagulation in the removal of tonsils at one time had reached the status of a fad with the laity as well as with some members of the profession itself. There arose a tremendous demand on the part of the public for this method of surgery out of all proportion to its merits. Fantastic claims as to simplicity of operation and lack of pain or bleeding have all proven untrue in actual practice. We have repeatedly, by the spoken as well as the written³ word, opposed the fallacious claims for a period of some 10 years. The recent literature on the whole is decidedly antagonistic to the method, and in all probability it is now going the way of most

medical fads. We have been impressed with but one indication for its use, namely, in the removal of tonsillar tags and lymphoid hypertrophy remaining after orthodox surgery. The present status of this method is well presented by Roberts,⁵⁰ who finds that the tonsil is not and in all probability may not be entirely removed by surgical diathermy. Secondary hemorrhage is not uncommon and postoperative pain is present as with the orthodox operation. In addition, infection and edema are quite frequent and in many cases the incomplete removal by diathermy may necessitate surgery subsequently. Mock,⁵⁶ in a similar vein, states that when the public learns of the dangers and complications incident to this method and especially of the possibility of leaving a buried focus of infection behind, it will undoubtedly shun it. In a report on their experience with the method, Shambaugh and his associates⁵⁵ find that it is not painless and that secondary hemorrhage can occur, and there is uncertainty as to the total removal of the tonsil. Finally Yonker,⁶⁷ in a thorough review of the subject, concludes that the results are unsatisfactory, and expresses his doubts as to any indication for its use.

Roentgen Ray Therapy of Chronic Tonsillitis. There has been a renewed interest in the Roentgen ray treatment of chronic tonsillitis. In a report on 32 patients that were followed up out of 47 treated by this method, Hasenjager¹⁵ believed there was a cure in 23, improvement in 5 and no benefit in 4. He believes it can be used in all cases in which surgery is contraindicated with the exception of children under 2 years. Hess¹⁷ reported a cure in 68 % of his 31 cases. He believes that the benefit was due to the destruction of the lymphoid cells. In some 54 children with recurrent attacks of tonsillo-adenoiditis, Niemeyer⁴¹ was enabled to observe a freedom from recurrence for over 2 years in about two-thirds of the cases and a milder attack in the remaining third. However, one scientific investigation seems to throw some doubt as to the validity of these admittedly clinical deductions—22 young men were subjected to irradiation of one of their tonsils, with proper protection to the other by Wolff.⁵⁶ Histologic examination of both tonsils removed later revealed no noteworthy difference between the irradiated and non-irradiated tonsil.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF APRIL 19, 1937

The Chemotropic Attraction of Leukocytes by Fraction of Streptococcus Hemolyticus. H. M. DIXON, MORTON McCUTCHEON, and E. J. CZARNETZKY (Laboratories of Pathology and Bacteriology, University of Pennsylvania). Previous studies have shown that the chemotropic attraction of neutrophils to bacteria *in vitro* is brought about chiefly by substances given off by the bacteria. The present

experiments represent an initial step in identifying such substances, by testing the chemotropic effect *in vitro* of certain fractions of *Strep. hemolyticus*.^{*} These fractions were: (1) A labile antigen consisting of a protein-carbohydrate complex, which, on injection into rabbits, produces specific agglutinating and phagocytosis-promoting antibodies; (2) a protein-free, non-antigenic, crystalline, stable hemolysin; (3) a carbohydrate (fairly pure and freed of protein). Each of these 3 substances was adsorbed on kaolin (which by itself does not attract leukocytes) and was then tested as a source of attraction for rabbit neutrophils *in vitro*. The leukocytes were obtained by injecting physiologic saline solution into the peritoneal cavity; the exudate was mixed with plasma, and a drop of the mixture was allowed to spread between slide and coverslip, with the coated kaolin particles in the center. Under the microscope, it was observed that leukocytes were strongly attracted to the particles coated with the labile antigen, but not to those coated with the other 2 fractions. It is concluded that of the 3 fractions of hemolytic streptococcus tested, the one which calls forth phagocytosis-promoting antibodies is also the substance that attracts leukocytes to the bacteria, thus making possible their phagocytosis.

A Chemotactic Substance Derived From Epithelium. DANIEL SILVERMAN (Laboratory of Pathology, Jefferson Medical College). Studies on chemotaxis were made by direct observation of leukocytic behavior according to McCutcheon's technique. Normal human skin, mechanically pulped without contact with water, showed strong chemotropism, a coefficient of $+0.83$. The chemotropic substance was dissolved out of pulped skin by extracting in hot water; skin pulp so treated showed no chemotaxis—a coefficient of $+0.05$. Chemotropism was demonstrated in the extract by evaporating the latter and soaking the previously extracted pulp in the concentrate. On testing this, a coefficient of $+0.77$ was obtained. The extract gave positive reactions for protein and free amino acid, but negative reactions for carbohydrate and histamine. A solution of histamine phosphate, tested in the same manner as the watery extract of skin, showed only slight chemotropic property—a coefficient of $+0.25$. Our results with preparations of *Staph. aureus* (coefficient $+0.61$) compared favorably with McCutcheon's results.

It is concluded that normal human skin contains an actively chemotropic substance (or substances), which is water-soluble and thermostable and which may be responsible for the behavior of leukocytes in inflammation following non-infected injuries. In infected areas the chemotaxis may depend in part on bacterial substances and in part on substances derived from the injured tissues.

The Synthesis of Octopine (Pectenine). J. LOGAN IRVIN and D. WRIGHT WILSON (Laboratory of Physiological Chemistry, University of Pennsylvania). Two years ago Drs. Moore and Wilson reported before this Society the isolation from scallop muscle of a compound which they later named pectenine. The description of properties given

^{*} For the method of preparation of these fractions see Mudd, S., Czarnetzky, E. J., Pettit, H., and Lackman, D.: Labile Bacterial Antigens and Methods for Their Preparation and Preservation, Proc. Am. Philos. Soc., in press.

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by Moore and Wilson, similar in most respects with that presented by Morizawa in 1927 for octopine, differed in that they had found that their free compound formed a neutral solution in water while Morizawa reported that his material was strongly alkaline. Recently Mayeda has shown that octopine monopicrate gives an acid reaction to Congo red which is in agreement with the observation of Moore and Wilson upon pectenine and indicates that Morizawa was in error. We therefore believe our compound to be octopine.

The structure of octopine was studied by Moore and Wilson who concluded that the compound is probably arginine, the α -amino group of which is joined to the α -carbon atom or propionic acid. In order to confirm this structure, we have carried out a synthesis involving a reaction between d-arginine and d, l- α -bromopropionic acid. Comparisons were made between the synthetic and natural materials in the free state and in the form of two salts. The results indicate that partially inactive octopine was synthesized. We plan to treat d-arginine with optically active bromopropionic acid in order to obtain the naturally occurring isomer.

Observations on the Effect of Adrenalectomy on the Hypertension Produced by Kaolin. W. A. JEFFERS, M. A. LINDAUER, and F. D. W. LUKENS (Robinette Foundation, Cox Institute, and Pepper Laboratory, University of Pennsylvania). Arterial hypertension was produced in 9 dogs. Four of these survived the removal of both adrenal glands. One animal exhibited a fall in blood pressure to normal following the second adrenalectomy. This fall was interpreted as being a remission from the effect of kaolin, since 3 other dogs showed a persistent hypertension after bilateral adrenalectomy as long as adrenal insufficiency was averted.

These experiments appear to confirm the negative rôle of the adrenal medulla in the maintenance of hypertension from kaolin. The cortical extract seemed to function merely to avert adrenal insufficiency, thus allowing the mechanism of hypertension to operate.

The Effect of Duodenal Stimulation in Man Upon Alimentary and Adrenalin Hyperglycemia. HARRY SHAY, J. GERSHON-COHEN, and SAMUEL S. FELS (Samuel S. Fels Research Fund and the Gastrointestinal Division, Medical Service I, Mt. Sinai Hospital). From an attempt to study glucose absorption in the human stomach by our method^{*} of producing pyloric closure through duodenal stimulation, we were led to consideration of the problem embodied in the title. The data we obtained indicate that: (1) Glucose, at least in high concentration, may be absorbed by the human stomach; (2) duodenal stimulation by hydrochloric acid will prevent a rise in blood sugar even though the amounts of sugar absorbed would ordinarily raise the blood sugar level; (3) the same effect was observed in a diabetic patient but did not occur in a very severe diabetic with a calcified pancreas; (4) the prevention or counteraction of alimentary hyperglycemia by duodenal stimulation is shown to be not a function solely of hydrochloric

^{*} Shay, H., and Gershon-Cohen, J.: Experimental Studies in Gastric Physiology in Man: II. A Study of Pyloric Control: The Rôles of Acid and Alkali, Surg., Gynec and Obst., 58, 935, 1934.

acid. Other agents which could stimulate the duodenal mucosa were equally efficacious. Thus similar results were obtained with fat, hypertonic solutions or sodium chloride and sodium bicarbonate, and of glucose itself; (5) while duodenal stimulation could prevent alimentary hyperglycemia, peculiarly enough, it did not carry the depression of glucose concentration below the fasting level. These observations are similar to those of Laughton and Macallum who found that their duodenal extract did not reduce the blood sugar below the normal resting level after induced hyperglycemia; (6) duodenal stimulation did not alter the normal fasting blood sugar level; (7) duodenal stimulation failed to prevent or decrease the hyperglycemia incident to adrenalin injection.

From a study of the literature on the effect of duodenal extracts and their possible method of action, we believe there is adequate evidence to show that their action is not due to secretin or to an insulin extract from the duodenum. It would appear to depend, in the dog, upon a combination of islet stimulation and direct action of a duodenal hormone upon glucose metabolism. From the results reported in the depancreatized animal, the direct action is the essential one. From our data in severe diabetes, it would seem that, in man, the duodenal mechanism is essentially concerned with islet stimulation. It would seem, therefore, that little could be expected from the use of duodenal extracts in the treatment of diabetes in man. In the mild cases of diabetes some effect from islet stimulation; in the severe diabetics probably no effect or even an injurious one by stimulation of already severely damaged islets.

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